FEBRUARY, 1951
VOL. III NO. 2

Circulation

The JOURNAL of the AMERICAN HEART ASSOCIATION

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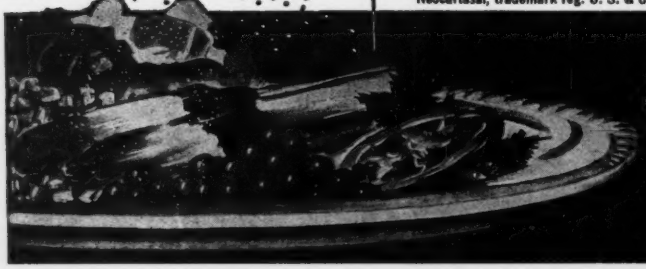

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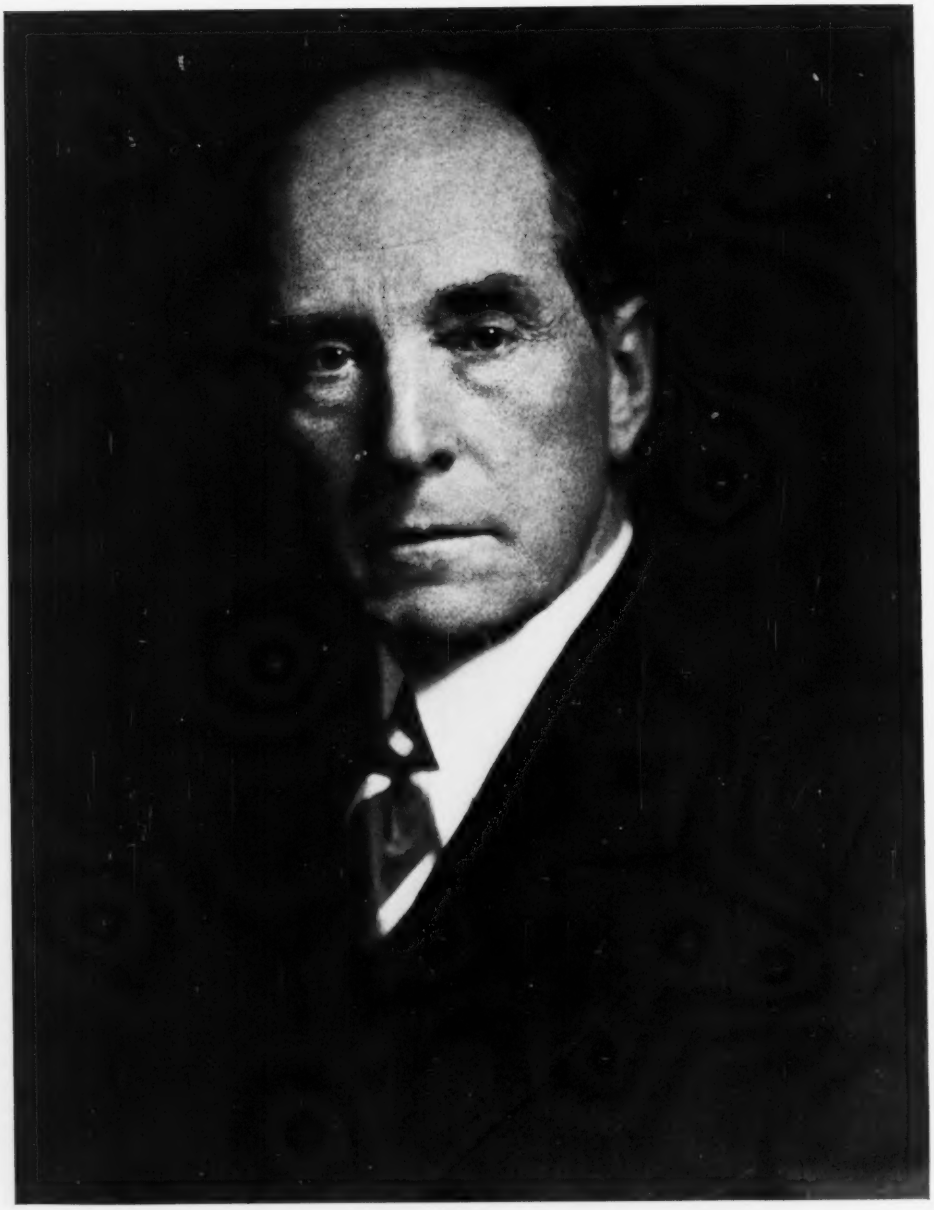

LEWIS ATTERBURY CONNER
1867–1950

Circulation
The Journal of the American Heart Association

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Lewis Atterbury Conner, 1867–1950

ON DECEMBER 4, 1950, at The New York Hospital, death came to one of the most distinguished of American physicians. His 83 years had been rich in accomplishment and his life and acts had merited the affection and esteem of the many students and colleagues whom he had taught and influenced.

Dr. Lewis Atterbury Conner was born in New Albany, Indiana. At 21 he received the degree of Bachelor of Philosophy from the Sheffield Scientific School of Yale University. Three years later he was graduated from the College of Physicians and Surgeons of Columbia University and was awarded a position as House Officer at The New York Hospital, thus commencing an association which was to extend over more than half a century. In 1898 he was selected as a member of the original faculty of Cornell University Medical College. Two years later, at the early age of 34, he was appointed Professor of Clinical Medicine, a position which he occupied until 1916, when he succeeded Dr. W. Gilman Thompson as Professor of Medicine.

Over the course of years Dr. Conner's interests and influence embraced many activities. He served as a private in the Spanish-American War and as a Brigadier General in the Army Medical Reserve Corps during the First World War. He was a friend and advisor of John Masterson Burke and was responsible perhaps more than any other for the concept and development of the Burke Convalescent Home.

He was one of the Founders of the American Heart Association, and served as its president in 1924 and 1925. He was the first editor of the American Heart Journal.

Dr. Conner's pre-eminence as a teacher can be attested by all graduates of Cornell and by many others who came into even casual contact with his remarkable example and method. His learning, his clinical judgment, and above all his integrity, made him the idol of the students and particularly of those chosen young men who were permitted to work with him as interns or residents in the wards of The New York Hospital. To them and to those who have succeeded them, his acumen and skill have become an unforgettable legend.

Dr. Conner's influence was most felt by those who knew him best. The casual observer might be impressed by his poise and dignity and might regard him as reticent, reserved or even austere. With those who knew him best, he was a delightful companion. To those in trouble his reserve was not evident and he appeared at once as a warm, sympathetic friend and wise counsellor.

Dr. Conner never expected praise or gratitude, but it is pleasant to think that he was frequently honored and that many tributes were offered to him. As head of the Department of Medicine at Cornell University Medical College and Attending Physician and Chief of Service at The New York Hospital, he was guest of honor at the dinner given at the Waldorf-Astoria Hotel on April 21, 1932, to celebrate the union of the two institutions.

In the last year of his life he received the Gold Heart of the American Heart Association as one of its four living founders.

If he could know that this issue of *Circulation* is to be dedicated to him, he would be surprised and embarrassed but he would be pleased and deeply moved by the expression of the respect of his colleagues.

December 19, 1950 DAVID P. BARR

Tromexan—3,3′-Carboxymethylenebis (4-Hydroxycoumarin) Ethyl Ester

Experimental and Clinical Properties

By GRAFTON E. BURKE, M.D., AND IRVING S. WRIGHT, M.D.

The use of heparin and dicumarol has provided important information regarding the effectiveness and the difficulties of anticoagulant therapy. Neither, however, is an ideal anticoagulant; therefore a search for new substances with advantages over them must be continued. Tromexan, which is administered orally, appears to have the advantages of more rapid utilization and more rapid cessation of action than dicumarol, although the mode of action is similar in that it produces a hypoprothrombinemia. It does require accurate prothrombin tests for satisfactory clinical use. It appears to be less prone to producing hemorrhagic complications. Animal and clinical experiences with Tromexan are herewith presented.

THE VALUE of anticoagulant therapy in the treatment of thromboembolic disease has been established by many workers.[1–10] However, certain properties which prevent both heparin and dicumarol from being ideal anticoagulants have spurred the search for new anticoagulants which might have advantages over them.[11] Clinical and experimental reports concerning the anticoagulant activity of the 3,3′-carboxymethylenebis (4-hydroxycoumarin) ethyl ester (Tromexan*) have appeared from Czechoslovakia,[12] Switzerland,[13] England,[14] and France[15].

Working on the hypothesis that one reason dicumarol is poorly absorbed is the difficulty in splitting the coumarin molecules, Rosicky weakened the methylene linkage between the two coumarin groups by adding the carboxyl radical.[12]

Overman and Link had originally investigated the acid in 1940[16] but, finding that it was much less active than dicumarol, did not esterify the compound. The anhydride of dicumarol has been shown to be inert biologically.

According to von Kaulla, Reinis and Kubik[13] in 1948 first reported the synthesis of this new anticoagulant. In their animal experimental work they noted that the administration of the drug caused a rapid decrease in the prothrombin activity with a relatively quick return to initial values after cessation of administration. They reported that patients showed a similar response following the administration of a single dose of 900 mg. In their experience this dose caused a measurable prolongation of the prothrombin time within one or two hours, reaching a maximum in 12 to 24 hours.

Von Kaulla and Pulver[17] in subsequent experimental work reported that the minimal lethal dose of Tromexan was approximately 750 and 1000 mg. per Kg. of body weight for mice and rabbits respectively. (The minimal lethal dose for dicumarol was 150 to 250 mg. per Kg.). It was also noted that after feeding 100 mg. per Kg. of Tromexan daily to mice, death usually occurred within a range of 26 to 51 days. At autopsy pathologic changes, mainly fatty infiltration, were noted in the liver. Less frequently lesions of the same nature were found in the kidney. In rats daily doses of 50 mg. per Kg. could be tolerated well over a period of one month or more. On the basis of clinical experience they concluded that Tromexan was tolerated well but that it must be administered at

From the Department of Medicine of Cornell University Medical College and The New York Hospital, New York.

This work was carried on under the auspices of the Committee on Anticoagulants of the American Heart Association and aided by grants from the Kress Foundation, the Lasker Foundation, the Hampil Foundation and the Hyde Foundation.

* Known as Pelentan in Czechoslovakia. Tromexan is sometimes referred to as DEA, from an alternate name, 4,4′-dihydroxydicumarinyl ethyl acetate. The Tromexan was supplied through the courtesy of Geigy, Inc.

approximately three times the dosage level of dicumarol in order to achieve a corresponding prolongation of the prothrombin time.

These workers[17, 18] also studied the pharmacology of the drug and demonstrated its breakdown into two degradation products: (1) Tromexan acid A, with a melting point of 216 C. and (2) Tromexan acid B, with a melting point of 171 C. They isolated these relatively inactive and nontoxic metabolic products in significant quantity from the urine. They also described a method for the quantitative determination of Tromexan in serum and in urine by coupling the drug with diazotized paranitroaniline at a *p*H of 6 to form a yellow dye. Following separation from the serum protein, Tromexan was extracted with benzene and was measured colorimetrically. This method can be applied to other coumarins. Tromexan itself, as well as its degradation products, is measured by this method. Throughout the above work it was found that rabbits tolerated Tromexan better and that it was more rapidly absorbed than dicumarol. The maximum blood concentration of the durg was somewhat less for Tromexan than for dicumarol with the same mg. dosage. The elimination of Tromexan was tested by giving 900 mg. to 4 patients. Maximum concentration in the serum was obtained at three to six hours. No Tromexan could be determined in the serum 24 hours after administration whereas traces of dicumarol could be detected as long as seven days after administration.

Reinis and Kubik,[13] de Nicola,[19] Pulver and Von Kaulla[18] and Della Santa[20a] all described additional clinical experience with Tromexan in the therapeutic management of thromboembolic disease. The dose used varied from 900 to 1200 mg. for the first two days, followed by a maintenance dose of 300 to 900 mg. daily. They originally gave this in a single daily dose but later concluded that the best method of administration was in the form of a tablet of 300 mg. three times a day.

Burt, Wright and Kubik[14] in England reported experiences with the use of Tromexan in 126 cases of thromboembolic disease. They too used the dose of 900 to 1200 mg. for the first two days followed by maintenance doses of 300 to 600 mg. In most instances a prothrombin percentage of 20 to 30 per cent was maintained. In some a level of 40 to 50 per cent was used. Daily prothrombin times were usually determined but experience suggested that once a maintenance dose had been established, determination on alternate days was sufficient. The period of treatment averaged 11 days but in 1 patient the prothrombin level was maintained at from 20 to 40 per cent for 10 months. In over 80 per cent of the cases the prothrombin activity decreased to at least 50 per cent within 36 hours and returned to normal within the same period after discontinuance of the drug. In 20 patients evidence of this response lasted for 60 hours or more. Slow initial response was not, however, invariably followed by prolonged effect. Postoperative patients as well as post-

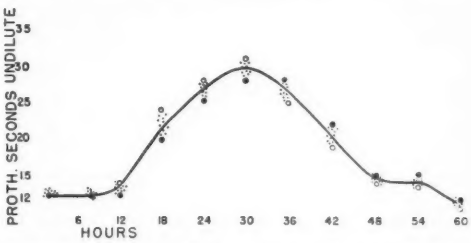

FIG. 1. Prothrombin curve following single dose of 400 mg. of Tromexan to rabbits.

partum patients were also treated. No excess puerperal or postoperative hemorrhage was observed in cases treated for varying periods following operation or delivery. In addition they noted that infants suckled by mothers receiving Tromexan manifested no bleeding tendencies.

Because of these European reports,[12–15, 17–20b] the experimental and clinical evaluation of Tromexan was undertaken at New York Hospital-Cornell Medical Center. A preliminary report of our early experience has appeared.[21]

STUDIES IN ANIMALS

As shown by Overman, Stahmann, Link and their co-workers[22a, b] with dicumarol there is an individual variation in rabbits and hence the animals used were standardized according to the technic described by them. By this means resistant animals were eliminated from the

series. A total of 36 rabbits were fed a sodium hydroxide solution (*p*H 11) of Tromexan in doses of 100, 200, 300, 400, 500, 600 mg. by stomach tube in a single dose. Prothrombin times were done at six hour intervals around the clock according to the Link-Shapiro technic. Determinations were twice checked by different technicians, and the samples were treated as unknowns. The results are tabulated in figure 1. No changes were noted in the first six hours. Slight elevations were noted in rabbits at the end of 12 hours, while at 18 and 24 hours consistent and reproducible prolongation of the prothrombin time was evident. The normal time in rabbits, 10.5 to 11.5 seconds, was doubled in a period of 18 to 24 hours, with average readings of the undiluted plasma of 22 at 24 hours and of 26 to 35 at 24 hours depending upon the dose. It was noticed that with increased dosage there appeared to be a total increased rise in the prothrombin time as well as a prolonged total excretion time. With increased doses the prothrombin rose more precipitously.

TABLE 1.—*Thromboembolic Diseases Present in Patients Treated with Tromexan.*

	Total
Thrombophlebitis without embolism	37
Legs (deep and superficial)	34
Arm (axillary vein)	3
Antepartum phlebitis	3
Thrombosis with embolism to lung	8
Peripheral embolism (rheumatic heart disease with auricular fibrillation)	3
Saddle embolus	1
Popliteal embolism	2
Cerebral embolism	2
Cerebral thrombosis	2
Retinal vein thrombosis	1
Myocardial infarction	48
Arteriosclerosis obliterans	6
Thromboangiitis obliterans	2
Total	112

In addition, mice and rats were fed Tromexan. The half lethal dose for mice was found to be 750 mg. per Kg., and for rats and rabbits, 1500 to 1800 mg. per Kg. Rats fed 100 mg. doses daily by stomach tube for 14 to 20 days failed to show any evidence of toxic symptoms.

STUDIES IN MAN

Twenty-four normal individuals used as controls were first studied with arbitrarily selected single doses of Tromexan of 1200, 1500 and 1800 mg. Twenty-four hours after the administration of single doses of 1500 to 1800 mg. the prothrombin time was found to have uniformly reached a level of 20 to 30 seconds (undilute plasma) and 65 to 100 seconds (dilute plasma). The control readings were 15 seconds ± 1.0 second with undilute plasma and 38 seconds ± 2 seconds with dilute plasma. With doses of 1200 mg. correspondingly lower levels were achieved. With the undilute plasma method consistent prolongation of the prothrombin times was obtained in the minimum time of 15 to 18 hours. However, in some cases slight elevation of prothrombin time in the undilute plasma and elevation of from 6 to 12 seconds in the dilute plasma was found within 12 hours following the initial dose. In the normal subjects no evidence of toxicity was found. Following a single dose the prothrombin time returned to normal within 48 to 60 hours.

In order to evaluate Tromexan clinically, a number of patients with thromboembolic disease were treated. These included a variety of conditions (table 1), chief among which were peripheral thrombophlebitis of the veins of the extremities, with and without pulmonary infarction, and coronary occlusion with myocardial infarction. The following studies were conducted on each patient before, during and after the use of Tromexan: daily urine examinations and periodic phenolsulfonphthalein tests; bromosulfalein tests; cephalin flocculation; thymol turbidity; total protein and albumin-globulin ratio; the alkaline phosphatase determinations; counts of the red and white blood cells; estimation of hemoglobin; determination of erythrocyte sedimentation rate and examination of stools for occult blood. Three of 112 cases showed evidence of microscopic hematuria while taking the drug. In all 3, however, there was evidence of pre-existing renal disease. Further discussion of these cases will follow.

Four patients showed symptomatic or chemical evidence of toxicity. One patient with liver disease showed slight alteration with the cephalin flocculation test and there was also a

slight alteration of the albumin-globulin ratio. These were known to be altered prior to the onset of therapy and following the cessation of Tromexan they returned to their previous abnormal levels.

Following an initial dose of 1200, 1500 or 1800 mg. the prothrombin time rose as indicated in figures 2, 3, and 4. A maintenance dose

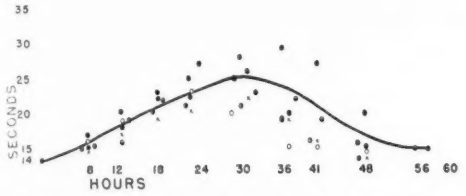

FIG. 2. Mean curve of prothrombin times in 6 normal subjects following single dose of 1200 mg. of Tromexan.

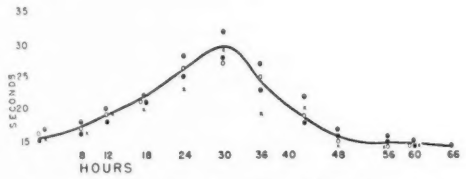

FIG. 3. Mean curve of prothrombin times of 4 normal subjects following single dose of 1500 mg. of Tromexan.

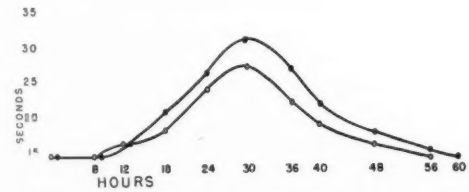

FIG. 4. Mean curves of prothrombin times after 1200 and 1500 mg. of Tromexan. Determinations run successively on same normal subject.

of 600 to 900 mg. per day was given. For the most part this was given in a single dose, and it should be emphasized that a period greater than 24 hours should not elapse between the administration of each dose if a therapeutic level is to be maintained. In individuals who showed marked fluctuation in their daily prothrombin times, divided doses of 300 mg. three times a day or 600 mg. twice a day were given with satisfactory results. Rare individuals required doses as high as 1200 mg. twice a day. About 15 to 20 per cent of the patients studied required this split dosage schedule (see figs. 5 and 6). Cases which showed fluctuations in daily levels were placed on the split doses and were well maintained. In only 1 case was it noted that the prothrombin time could not be considered to have been held within therapeutic range and in this patient there was extension

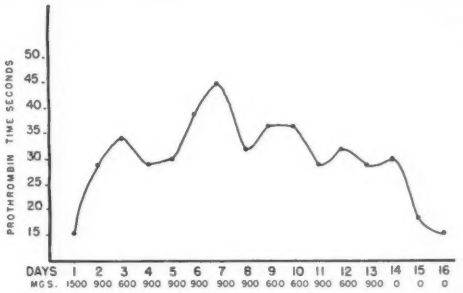

FIG. 5. Prothrombin times of a patient with thrombosis of axillary vein given single daily doses of Tromexan. A good clinical and therapeutic response.

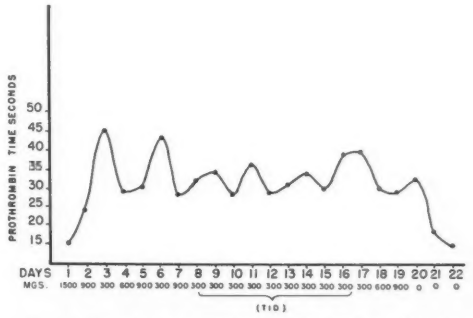

FIG. 6. Results in a patient with thrombophlebitis of femoral vein who was not regulated by a single dose; three daily doses were therefore given.

of the thromboembolic process. This individual with a pulmonary infarction had clinical evidence of extension or a new pulmonary embolus to the lungs after three days of therapy. The dosage was increased to produce a satisfactory hypoprothrombinemia and thereafter the patient had an uneventful clinical course. The patients on Tromexan showed a good clinical response which was fully comparable to that experience with dicumarol.

Two patients showed a rather precipitous

rise in their prothrombin time following the administration of Tromexan over a period of two or three days. Both these patients had overt signs of renal disease with elevated blood urea nitrogen, fixed concentrations of specific gravity of the urines and other evidence of a chronic glomerulonephritis. One patient showed a rise of the prothrombin time (undilute plasma) to 120 seconds while on a maintenance dose of 900 mg. per Kg. per day. Prothrombin time was then determined at six hour intervals and the prothrombin time rapidly returned toward normal. Twenty-four hours following the high peak of 120 seconds the prothrombin time was 26 seconds; 30 hours later, 22 seconds; and in 36 hours it was normal, namely 15 seconds with undilute plasma. There was no evidence of bleeding and no vitamin K was administered.

One patient was mistakenly given an extra dose of 1200 mg. of Tromexan and thus received 3000 mg. in 24 hours; his prothrombin time rose to 66 seconds. This was watched carefully and within 24 hours had returned to 23 seconds.

The above cases suggest that vitamin K will rarely be necessary in cases of accidental overdosage (unless evident hemorrhage is present) because of the rapid excretion rate of Tromexan and the fact that the prothrombin time returns to the normal range in a relatively short period of time. However, the effect of vitamin K was studied in 3 normal patients. Tromexan was pushed so that the prothrombin time rose to levels of 35 to 53 seconds at which points 50 mg. of water soluble vitamin K were given intravenously. The prothrombin time returned to within normal limits in a period of 12 hours which is faster than we have noted if no vitamin K is given. Control studies on the same subjects without using vitamin K showed a return to normal from an average peak of 50 seconds after 24 to 48 hours. Vitamin K does apparently effectively combat the anticoagulant activity of Tromexan.

Discussion

These studies have confirmed the reports that Tromexan acts and is excreted more rapidly than dicumarol.[12–15, 17–20b] From the structural formula of this coumarin derivative it could be hypothecated that the weakening of the bond between the two coumarin groups would tend to make it more soluble and the addition of the carboxyl at this point would from the pharmacologic basis tend to make the drug more readily absorbed. This was been borne out by our clinical and animal experimentation. The metabolic route of excretion and absorption previously studied by Della Santa and von Kaulla[20a, b] is now being investigated by Brody, Shapiro and Weiner. Further pharmacologic studies are being carried on by Gruber in Philadelphia. On the basis of work done heretofore by Gianella and von Kaulla,[23] and others, and communications from Brody, Shapiro and Weiner* it appears that Tromexan probably has different routes of excretion and metabolic breakdown from dicumarol, and its method of detoxification is still obscure. The difference in potency between dicumarol and Tromexan may well be explained on this basis. Tromexan appears to be about one-fifth as potent as dicumarol on the basis of weight and hence four to five times the dose must be given. In addition, Tromexan is so rapidly absorbed that prothrombin time determinations done at 18 to 24 hours show a consistent prolongation. The toxicity of the drug appears less when compared in terms of therapeutic dosage with dicumarol. No patients showed any evidence of urticaria, rash, idiosyncrasy to the drug or intolerance except as cited. The tablets are bitter and should be swallowed intact. The dosage given in our series has ranged from 600 to 1800 mg. Occasionally an individual will be found who requires an even larger dose. We have found no cases who showed a true drug resistance by failing to respond to the careful administration of an increased dosage. The regulation of the patient on Tromexan is usually easier than that of the patient on dicumarol because each prothrombin test is a direct reflection of the dose given the previous day. If this time is too low the dose can be increased with a relatively prompt response. There is little cumulative effect of the drug, particularly if it is given in single doses at an interval of 24 hours, or less. In general, however, an interval greater than 24 hours should not elapse between

* Personal communications.

the administration of the drug if an effective level is to be consistently maintained. Certain individuals may require the drug at more frequent intervals. Our results differ from those of the European investigators in that we have been unable to show appreciable prolongation of the prothrombin time in six hours as they reported.

Conclusions

1. The coumarin derivative 3,3′-carboxymethylenebis (4-hydroxycoumarin) ethyl ester (Tromexan) produces a significant prolongation in the prothrombin time when administered in therapeutic doses.

2. It has approximately one-fifth the potency of dicumarol, when compared mg. per Kg., in terms of effect on the prothrombin time obtained.

3. Tromexan has a faster absorption and utilization rate than dicumarol as measured by the level of hypoprothrombinemia produced within 18 to 24 hours after the initial dose.

4. The duration of the anticoagulant effect is about one-half to one-fourth that of dicumarol.

5. Prothrombin times return to normal 48 to 60 hours after a single initial dose.

6. Satisfactory maintenance of a therapeutic level of hypoprothrombinemia can be achieved by single daily doses of 600 to 2400 mg. or a dose of 300 to 900 mg. administered in two or three divided doses.

7. The requirements are dependent on the individual response which must be determined by prothrombin tests.

8. In the presence of renal damage hematuria was noted in 3 cases.

9. Further alteration of abnormal liver function and the albumin-globulin ratio was noted in 1 case of liver disease.

10. Of 112 cases treated only the reactions cited under 8. and 9. were noted.

11. Further clinical trials, on a cooperative basis, are now in progress in order to evaluate its usefulness as a rapidly acting anticoagulant in the treatment of thromboembolic disease.

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Clinical Evaluation of Dicumarinyl Derivatives with a Metabolic Study of the Radioactively Labeled Anticoagulants in Animals

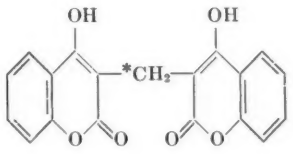
By Eric P. Hausner, M.D., Charles L. Shafer, M.D., Marion Corson, Ogden Johnson, Theodore Trujillo and Wright Langham

The common use of dicumarinyl derivatives for the treatment of thromboembolic diseases justifies further clinical evaluation of dicumarol and 4,4′-dihydroxydicumarinyl ethyl acetate [Pelentan, Tromexan, 3,3′-carboxymethylenebis (4-hydroxycoumarin) ethyl ester.]

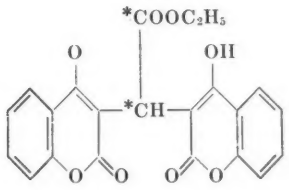
The need for a more thorough understanding of the pharmacodynamic action of dicumarinyl anticoagulants has prompted a study of their gross metabolism in animals, using C^{14}-labeled materials.

SINCE the introduction of anticoagulants for short and long term management of thromboembolic disease the search for a better anticoagulant has become more intensified. Heparin, dicumarol and the coumarin derivatives are the anticoagulants commonly used. Lately phenylindandione[1] and Paritol with its heparin-like action[2] have come into experimental clinical usage. Dicumarol, with its proved value as an anticoagulant, has the disadvantage of a long period of latency of action as well as a prolonged hypoprothrombinemic effect. The coumarin derivative, 4,4′-dihydroxydicumarinyl ethyl acetate [hereafter referred to as DEA; also known as 3,3′-carboxymethylenebis (4-hydroxycoumarin) ethyl ester; commercially available as Tromexan or Pelentan], widely described and favored in the European literature, is reported to have a shorter period of latency, a less sustained hypoprothrombinemic effect and is less toxic.[3–7]

The initial step in our study was the comparative clinical analysis of dicumarol and the coumarin derivative DEA in healthy subjects and in patients with thromboembolic disease. Further studies were conducted on animals with the two anticoagulants, using radioactively labeled materials.



I. DICUMAROL



II. DEA

Dicumarol and DEA were labeled with C^{14} in the positions indicated by the asterisks in formulas I and II respectively.† This method enabled us to study the absorption, metabolism and urinary excretion of the anticoagulants in relation to their hypoprothrombinemic effect.

Comparative Clinical Analysis of Dicumarol and DEA

Ten healthy subjects with normal liver function were given a single large dose of dicumarol. The dicumarol was administered in the early

This document is based on work performed at the Los Alamos Scientific Laboratory of the University of California under A.E.C. Contract W-7405-Eng-36.

Presented before the First International Cardiological Congress, Paris, France, Sept. 1950.

† At the time this work was in progress in our laboratory Lee and co-workers[8] independently labeled dicumarol with C^{14} and conducted studies of some of the aspects of the metabolism of this anticoagulant.

morning hours, usually following a light breakfast. The individuals were kept on a normal diet throughout the experiment. No other medication was permitted. Prothrombin levels were determined by Quick's method[9] for undiluted plasma prior to the administration of the drug, at 6 hour intervals for a period of 48 hours, and at 12 hour intervals from the forty-eighth through the ninety-sixth hour.

Curve *A* in figure 1 shows a steady decline in the prothrombin activity following the administration of a single dose of 400 mg. of dicumarol. In 34 hours average prothrombin activity was lowered to 30 per cent of normal,

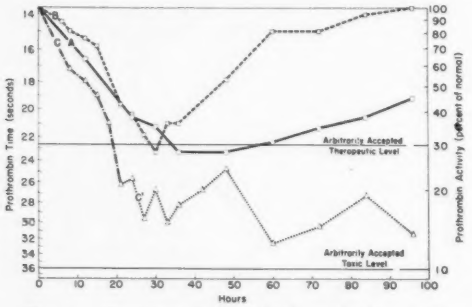


FIG. 1—Comparative clinical analysis of dicumarol and DEA in healthy human subjects and in patients with thromboembolic disease. *A*. The hypoprothrombinemic effect of a single dose of dicumarol (0.4 Gm.) in 10 healthy human subjects. *B*. The hypoprothrombinemic effect of a single dose of DEA (1.5 Gm.) in 20 healthy human subjects. *C*. The hypoprothrombinemic effect of initial (1.5 Gm.) and (*C'*) maintenance (0.3–0.6 Gm.) doses of DEA in 20 patients with thromboembolic disease.

the arbitrarily accepted therapeutic level. The maximal hypoprothrombinemic effect was observed at 36 hours. The prothrombin level remained below 30 per cent of normal activity for 24 hours. The return toward normal prothrombin values was gradual and at 96 hours the levels averaged 45 per cent of normal prothrombin activity.

Eight of the 10 subjects experienced mild and transient gastrointestinal symptoms.

Twenty healthy subjects with normal liver function were given a single dose of 1.5 Gm. of DEA. Experimental conditions were kept identical to those in the dicumarol group and prothrombin determinations were made at essentially the same time intervals following administration.

TABLE 1.—*Prolonged Management of a 45 Year Old Patient (#13587) with Acute Myocardial Infarction Treated with DEA.*

Time Schedule of Prothrombin Determination and Treatment		Prothrombin Time (sec.)	Prothrombin Activity % of Normal	Dosage DEA (Gm.)*
Day	Hour			
1	0	13	100	1.5
	12	15	80	
	18	20	41	
	24	27	20	0.3
2	30	28	18	
	36	34	11.5	
	42	31	14	
	48	32	13	0.3
3	60	31	14	
	72	21	36	0.3
4	84	42	6.8	
	96†	35	10.5	
5		31	14	0.3
		30	15	
6		23	29	0.3
		22	32	0.3
7		27	20	
		24	26	0.3
8		25	23	0.3
		65	2.4	
9		36	10	
		19	46	0.3
10		32	13	
		—	—	
11		25	23	0.3
		24	26	0.3
12		58	3	
		27	20	
13		21	36	0.3
		—	—	
14		30	15	0.3
		35	10.5	
15		26	21	0.3
		—	—	

* Medication was given after corresponding prothrombin values were reported.

† After the ninety-sixth hour prothrombin determinations were made twice daily unless otherwise indicated.

Curve *B* in figure 1 shows that the prothrombin level following the single dose of DEA declined at approximately the same rate as observed with dicumarol. However, 30 per cent of normal prothrombin activity was ob-

served at 28 hours. The maximal hypoprothrombinemic effect occurred at 30 hours. The prothrombin level remained below 30 per cent of normal activity for only 4 hours as compared to 24 hours for dicumarol. The return toward normal prothrombin levels was far more rapid than in the dicumarol group, and normal levels were approached at 60 hours following administration of a single dose of this drug.

Twelve patients with thrombophlebitis (complicated in three instances by pulmonary embolism), 6 patients suffering with acute myocardial infarction, 1 patient with thromboangiitis obliterans, and 1 with multiple sclerosis comprised the group of 20 patients treated with DEA. All patients received an initial dose of 1.5 Gm. of DEA as in the controls. Additional DEA was given after the twenty-first hour when needed for the maintenance of therapeutic hypoprothrombinemia.

Curve *C* of figure 1 shows an even more rapid decline in prothrombin activity following the initial dose of 1.5 Gm. of DEA than was observed in the control group. Prothrombin activity was found to be reduced to 30 per cent of normal at 19 hours, and in the majority of patients the maximal hypoprothrombinemic effect was reached in 27 hours. In the average patient 0.3 to 0.6 Gm. of DEA daily in divided dosages maintained the prothrombin activity well within the therapeutic range (curve *C'*). For the sake of brevity, curve *C-C'* shows values only throughout the first four days of treatment.

Prolonged therapeutic management with DEA in a patient with acute myocardial infarction is illustrated in table 1. This is a representative case in our series of 20 patients with thromboembolic disease treated with DEA.

Animal Experiments with C^{14}-Labeled Dicumarol and DEA

Methods. Each of 15 male albino rats (Sprague-Dawley) weighing approximately 200 Gm. was given an oral dose of 25 mg. of radioactive dicumarol (specific activity, 77,000 counts per second per mg.). The anticoagulant was administered via stomach tube followed by 2 cc. of 5 per cent ethanol in water. To ensure the greatest possible absorption the rats were fasted for six hours prior to the administration of the drug. Three of the animals were placed in all-glass metabolism cages of the type reported by Roth and co-workers[10] for the simultaneous collection of respiratory carbon dioxide, urine and feces. No significant radioactivity was found in the exhaled carbon dioxide up to 24 hours after oral administration of dicumarol so the remaining animals were placed in open metabolism cages for the collection of urine and feces samples only. The animals had free access to water throughout the experiment, and to food after an interval of 12 hours.

The rats, in groups of three, were sacrificed at 6, 12, 24, 36 and 48 hours. The prothrombin levels were estimated on blood obtained by heart puncture just prior to sacrifice, employing the Link-Shapiro modification of Quick's method.[11] The estimations were made on 25 per cent plasma using .025 molar calcium chloride solution. Analyses for radioactivity were made in all groups on the following tissues: heart, lungs, liver, kidneys, entire gastrointestinal tract and contents, skin (including hair), feces, urine, blood and the remains, which included the carcass and all organs not mentioned above. A more detailed study was made of the 24 hour group. In addition to the above mentioned tissues, bone, bone marrow, muscle, spleen, thymus, testes, and brain were analyzed for radioactivity.

In order to obtain homogeneous samples, the gastrointestinal tract and contents, the feces and the remains were homogenized with normal sodium hydroxide in a Waring Blendor and made up to a given volume with water. Uniform samples of all other tissues were obtained by freezing each tissue with liquid nitrogen and crushing it to a powder while still frozen. After thawing, the powdered tissue was mixed thoroughly and aliquots taken for analysis. All samples were oxidized to carbon dioxide, using a modification of the Van Slyke chromic acid oxidation procedure.[12] The carbon dioxide was collected quantitatively in normal sodium hydroxide, precipitated as barium carbonate, plated and counted with a thin mica window Geiger tube using essentially the same technics as described by Dauben and associates.[13]

Blood samples were plated directly[14] and counted. Direct activity measurements were also made on plasma and on washed cells. Urine samples were collected at 6 hour, and feces at 12 hour intervals. The individual samples were plated directly for relative activity measurements; pooled samples were then oxidized and analyzed to give the total radioactivity excreted in urine and feces during the period of the experiment.

Studies using radioactive DEA were made in essentially the same manner as described for radioactive dicumarol.

The C^{14}-labeled DEA (specific activity, 18,000 counts per second per mg.) was given in a dose of 100 mg. to each of 12 male albino rats weighing approximately 200 Gm. each. Since the 100 mg. dose

was too large to be given in one single administration with the stomach tube, it was administered in two 50 mg. portions 30 minutes apart. Samples of urine, feces, and expired carbon dioxide were collected and the animals sacrificed in groups of three at 6, 12, 24 and 36 hours.

One-dimensional filter paper partition chromatography[15] was used to separate the metabolic products of dicumarol and DEA in urine, plasma, and in extracts of feces and the gastrointestinal tract plus its contents. Samples representing 100 counts per second were placed in a transverse line on strips of Whatman no. 1 filter paper 2 by 42 cm. The biologic fluid was applied to the strip in very small amounts by means of a micropipette, allowing the fluid to dry between additions. The chromatogram was then developed in an upright, closed column in a solvent system of butanol-methanol (3:1) saturated with water. Fourteen different solvent systems were tried and the system of butanol-methanol-water was found to be most satisfactory. After development, the chromatograms were removed from the columns and allowed to dry. Autoradiographs were made from each chromatogram by exposing the filter paper strips to Blue Brand x-ray film for two weeks.

Results. Gross metabolic studies in 15 rats following oral administration of 25 mg. of C^{14}-labeled dicumarol and in 12 rats fed 100 mg. of C^{14}-labeled DEA gave an average recovery of approximately 99 per cent of the administered activity. The total recoveries ranged from 96.5 to 101.4 per cent (see tables 2 and 3).

An average of 71.9 per cent of the activity administered as dicumarol and 71.6 per cent of that administered as DEA was recovered from the feces plus the gastrointestinal tract and its contents. Autoradiographs of the filter paper chromatograms of fecal and intestinal extracts indicated that the activity in the feces and gastrointestinal tract was predominantly in the form of the original material.

If the net absorbed dose is taken as the amount of activity found in the tissues (excluding the gastrointestinal tract), urine and expired carbon dioxide, then the data in tables 2 and 3 show an average net absorption from the intestine of 27.1 per cent of the administered activity in the case of dicumarol and 27.5 per cent in the case of DEA. In both cases maximal net absorption occurred during the first six hours after administration. These data indicate that DEA, when given orally to rats, is not absorbed in significantly greater percentage nor at a significantly faster rate than is dicumarol.

Although filter paper partition chromatograms indicated that the activity in the intestinal tract and feces was probably predominantly in the form of the administered compounds, absorption from the intestine must be expressed as *net* rather than *total* absorption because of the possibility of excretion of absorbed material back into the gut via the hepatobiliary system. Studies by Lee and co-workers[8] of the distribution of C^{14} activity following *intravenous* administration of labeled dicumarol to mice and rabbits showed appreciable amounts of activity in the bile and intestinal contents. Their report prompted us to conduct a preliminary study of the excretion of activity via the kidney and intestinal tract following intravenous injection of labeled dicumarol and DEA into rats. Twenty-four hours after injection of 5 mg. of C^{14}-dicumarol into the tail vein of each of 3 200 Gm. rats, an average of 32.6 per cent of the activity was found in the feces plus the intestinal tract and its contents and 15.8 per cent was found in the total urinary excretion. This gave an over-all excretion of 48.4 per cent of the administered activity. An identical experiment using 5 mg. of C^{14}-DEA showed 49.7 per cent of the injected activity in the feces plus the intestinal tract and its contents and only 4.2 per cent in the urine giving a total excretion of 53.9 per cent.

The data in table 4 show the relationship between C^{14} activity in some of the tissues and organs, and in urine and expired air at various times after the oral administration of labeled dicumarol and DEA. Because of the fluctuations among individual animals in the net amounts of radioactivity absorbed from the gut during a given time interval, the results were computed as per cent of net absorbed activity per organ or tissue rather than as per cent of the administered dose. Table 5 shows the same data given in table 4 but expressed as per cent of the net absorbed activity per Gm. of tissue or organ.

These data show that the maximal tissue concentration of radioactivity occurred at or before six hours. The liver, blood and kidneys showed the highest concentration per Gm. of

tissue (table 5). It should, of course, be pointed out that some of the activity found in the various tissues was due to the activity of the blood contained therein since organs were not perfused. However, as much of the blood as possible was withdrawn by heart puncture in order to lower the blood content of the tissues.

Of the total radioactivity present in the blood of rats given oral doses of dicumarol, 97 to 99 per cent was found in the plasma fraction and the remaining 1 to 3 per cent was found in the cells. The ratio of the activity in the plasma to that in the cells remained unchanged throughout the 48-hour study. With DEA, on the other hand, 82 to 91 per cent of the total radioactivity in the blood was found in the plasma fraction at 6 and 12 hours and 9 to 18 per cent in the cells. The ratio of plasma to cell activity changed gradually with time until at 24 to 36 hours the per cent of activity in the plasma was the same as for dicumarol (97 to 99 per cent).

The data in table 5 show that up to 24 hours no significant activity was found in the exhaled carbon dioxide of rats given C^{14}-dicumarol; therefore, collection of respiratory air was discontinued with the 36 and 48 hour groups. However, in rats given C^{14}-DEA, approximately 0.1 per cent of the total administered radioactivity was found as expired carbon dioxide during the first 6 hours, and a total of 0.6 per cent during the first 24. Samples of respiratory air were collected at 30 minutes, 1, 2 and 3 hours, and thereafter every 3 hours for the first 24 hours. The activity in expired air increased to a maximum in the 6 to 9 hour sample. Computed on the basis of per cent of net absorbed dose, the following aggregate values were obtained: 0.53 per cent at six hours; 1.44 per cent at 12, and 2.58 per cent at 24 hours (table 4). The extrapolated estimate for the 36 hour carbon dioxide value was approximately 3.6 per cent of the absorbed dose.

Comparison (table 4) of the C^{14} activity in the tissues of the dicumarol-treated group with that of the DEA-treated group at the various times reveals a rather significant point. The changes in tissue activity with time are similar but for a lag of 6 to 12 hours in the case of the dicumarol-treated animals. As an example, the average value for the blood of the dicumarol group at 24 hours was 7.77 per cent as compared with 7.53 per cent for the blood of the DEA group at 12 hours. The longer tissue retention of C^{14} in the dicumarol series was also reflected by a slower rate of urinary excretion.

The above observation is shown more clearly in figure 2. In this graph the urinary excretion rates of C^{14} activity following oral administration of the labeled compounds were compared by plotting the per cent values of the net absorbed activity excreted during successive six hour time intervals. The corresponding change in the activity retained by the body is shown in the upper curves of figure 2. Retention curves were established merely by subtracting the activity excreted in the urine (ignoring the small amount excreted as carbon dioxide in the case of DEA) from 100 per cent of the net absorbed activity. The curves demonstrate an earlier drop in retained activity following DEA than following dicumarol. The earlier drop in tissue retention is obviously paralleled by a greater rate of urinary excretion during the first 12 hours. Table 4 shows that 61.4 per cent of the net absorbed activity was excreted in the urine during the first 12 hours following oral administration of C^{14}-DEA as compared with 20 per cent for C^{14}-dicumarol. Both groups of animals showed a maximum urinary output of activity during the 6 to 12 hour period (fig. 2).

Autoradiographs of the filter paper chromatograms are shown in figure 3. The autoradiographs for urine and plasma from C^{14}-dicumarol-treated animals indicate seven possible radioactive compounds in the urine and possibly four in the plasma. A control autoradiograph showing C^{14}-dicumarol indicates that one of the radioactive compounds in the urine and one in the plasma may be unchanged dicumarol or a compound sufficiently similar in structure to have the same partition characteristics in the solvent systems used for the separation. The relative densities of the bands give a rough indication of the relative amounts of the substances present. The relative densities of the bands of the plasma autoradiograph suggest that unchanged dicumarol may account for a major part of the activity in the plasma. The autoradiographs for urine and plasma from

DEA-treated animals show only three separate bands in the urine and only two in the plasma. Again the control autoradiograph of C^{14}-DEA indicates that some unchanged DEA may be present in both urine and plasma. The various bands observed in the chromatograms of urine and plasma for both drugs as illustrated in figure 3 were in evidence at the six hour interval and remained essentially unchanged for the duration of the experiment.

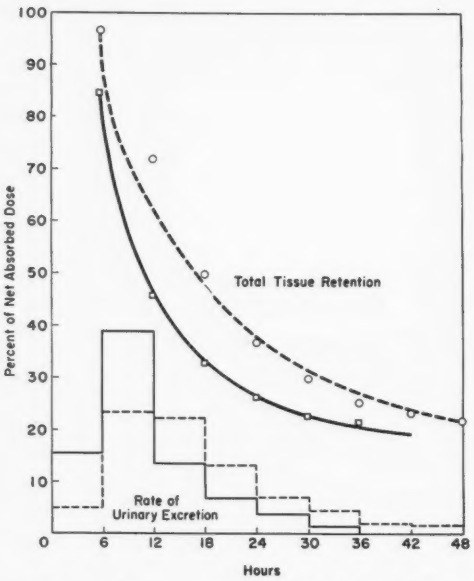


FIG. 2—Measurement of radioactivity following oral administration of C^{14}-dicumarol (dashed line) and C^{14}-DEA (solid line). Total tissue retention in relation to rate of urinary excretion.

It must be pointed out that the filter paper partition technic as applied in these studies is an indicator method only and is not meant to be taken as absolute. The difference in the number of bands shown by the chromatograms of the urine and plasma may be due to limitations in sensitivity of the method. The concentration of some of the metabolites in the plasma may be too low to be demonstrated chromatographically. Each band shown by the autoradiograph may result from a single radioactive substance or from two or more substances with very similar diffusion characteristics. Attempts to separate a mixture of C^{14}-dicumarol and C^{14}-DEA using fourteen different solvent systems were unsuccessful. Nevertheless, the material presented in figure 3 serves as an interesting preliminary observation regarding the detailed metabolism of DEA and dicumarol by the rat.

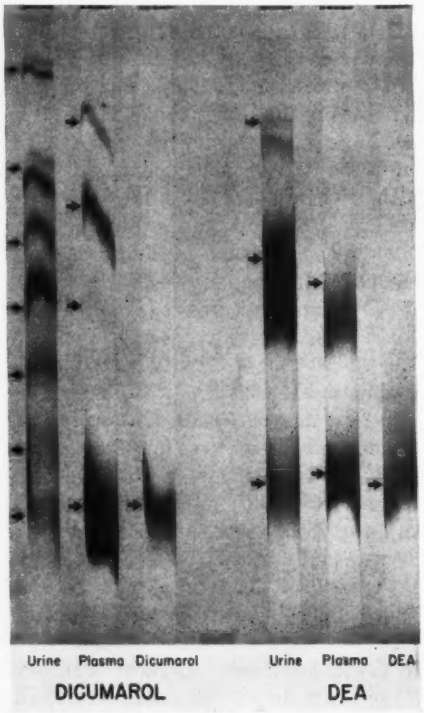


FIG. 3—Autoradiographs of filter paper partition chromatograms. Chromatograms of urine and plasma from animals treated orally with C^{14}-labeled dicumarol and DEA are compared with chromatograms of each of the labeled anticoagulants alone. The biologic fluid in each case was placed at the top of the chromatogram as indicated by a transverse broken line. The individual diffusion bands are indicated by arrows.

Prothrombin times were determined at 6, 12, 18, 21, 24, 27, 30, 36 and 48 hours following oral administration of 25 mg. of radioactively inert dicumarol and at comparable times after the administration of 50 mg. of inert DEA. A 50 mg. dose of inert DEA was used instead of 100 mg. (the dose comparable in hypoprothrombinemic effect to 25 mg. of dicumarol) because of the wide variation in response of rats to high

doses. With these dosages there were moderate variations in the hypoprothrombinemic response of rats to both dicumarol and DEA and it was necessary to use at least 5 animals per point. Response to DEA, particularly at higher effective dosage levels, was even more variable than response to dicumarol.

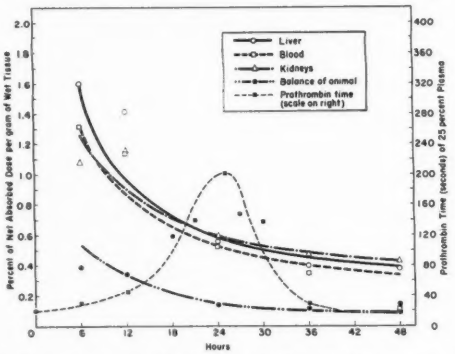


FIG. 4—Concentration of radioactivity in tissues as related to prothrombin activity following oral administration of C^{14}-dicumarol.

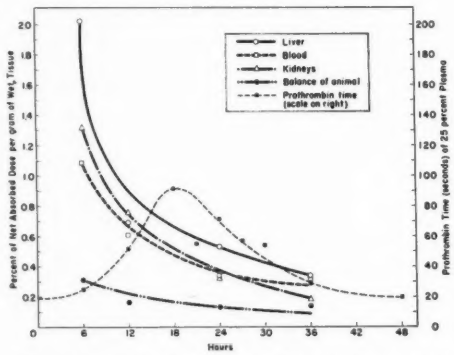


FIG. 5—Concentration of radioactivity in tissues as related to prothrombin activity following oral administration of C^{14}-DEA.

In figures 4 and 5 the hypoprothrombinemic response of rats to dicumarol and DEA is compared with the concentration of C^{14} activity in liver, blood, kidney and balance (remainder of the animal) at various times after oral administration of the labeled compounds. Prothrombin time in seconds, as a function of time after oral administration, was compared with the per cent of net absorbed activity per gram of wet tissue. The results of the dicumarol study are given in figure 4. This graph shows that the peak of the hypoprothrombinemic effect occurred at approximately 24 hours after administration. During this time interval the concentration of radioactivity in the various tissues and in the balance steadily decreased to approximately one-third of the concentration at six hours. The results following oral administration of DEA are shown in figure 5. Maximal hypoprothrombinemic effect occurred at about 19 hours after administration. Again the concentration of radioactivity in the various tissues and in the balance had decreased to approximately one-third of the six hour concentrations.

DISCUSSION

Clinical Observations. Our experience confirms the reports in the literature[3-7, 16] that DEA has a quicker and more transient hypoprothrombinemic effect in human subjects than has dicumarol. A single dose of 1.5 Gm. of DEA produced a therapeutic hypoprothrombinemia in our control series approximately six hours sooner than did a single dose of 400 mg. of dicumarol. It is interesting to note that therapeutic hypoprothrombinemia occurred at 19 hours in our series of DEA-treated patients with thromboembolic disease, as compared to 28 hours in our DEA controls. The therapeutic level in the controls was maintained for only 4 hours with DEA as compared to 24 hours with dicumarol. The return to normal prothrombin activity was far more rapid after the administration of DEA than after dicumarol. No gastrointestinal side effects were observed in our DEA group. Urinary and fecal excreta were analyzed for the presence of blood in the DEA group when prothrombin levels dropped below 10 per cent of normal activity. It was interesting to note that even with prothrombin times of 70 seconds evidence of bleeding was absent.

The management of patients receiving DEA frequently requires prothrombin determinations oftener than once a day for effective regulation of prothrombin levels. On the other hand, the management of patients with dicumarol is more easily controlled with less frequent prothrombin determinations. Although neither dicumarol nor DEA is an ideal

anticoagulant, DEA is somewhat superior to dicumarol in its speed of action and its less sustained hypoprothrombinemic effect.

Animal Experiments. The results of animal experiments using C^{14}-labeled dicumarol and DEA indicated that DEA had a slightly more rapid and more transient action than did dicumarol (figs. 4 and 5). The quicker action of DEA following oral administration does not seem to be attributable to a quicker or greater net absorption of the C^{14} activity from the intestinal tract (tables 2 and 3). In the case of DEA there does, however, seem to be a higher initial liver concentration and an earlier drop in the percentage of retained activity in the tissues of the animal, paralleled by a higher urinary excretion rate immediately following administration (fig. 2). In general, the slower rate of metabolic turnover of C^{14} activity following administration of labeled dicumarol may be responsible for its prolonged hypoprothrombinemic effect.

Maximal absorption and maximal concentration of activity in the liver, blood, kidney and balance occurred within six hours after the oral administration of both labeled dicumarol and labeled DEA (tables 4 and 5). In neither case was there any positive correlation between the time of maximal absorption or maximal concentration in the liver, blood, kidney and balance and the time of maximal hypoprothrombinemic effect of the drug (figs. 4 and 5).

The above observations indicate that the mode of action of dicumarol and DEA is essentially the same. The lack of positive correlation between maximal tissue concentration of C^{14} activity and maximal hypoprothrombinemic effect supports the postulate that the mode of action of dicumarinyl anticoagulants involves in some way an interference with the production of prothrombin by the liver.

Our observation of the failure of production of $C^{14}O_2$ from labeled dicumarol confirms the observations of Lee and co-workers,[8] who found no exhalation of C^{14} activity following intravenous administration of labeled dicumarol to mice. A small amount of $C^{14}O_2$ was produced from the doubly labeled acetate group in DEA

TABLE 2.—*Gross Distribution of C^{14} Activity in Terms of Per Cent of Administered Dose at Various Times after Oral Administration of C^{14}-Dicumarol to Rats.*

Distribution of Administered Dose	Time After Oral Administration*					Average Values
	6 Hr.	12 Hr.	24 Hr.	36 Hr.	48 Hr.	
Net Absorption,† % Administered Dose	32.94	33.55	23.90	17.47	27.49	27.07
G.I. Tract & Contents, % Administered Dose	66.44	61.65	16.35	3.94	2.29	30.13
Feces (Excreted), % Administered Dose	0.91	5.69	56.84	75.10	70.28	41.76
Total Recovery, % Administered Dose	100.29	100.89	97.09	96.51	100.06	98.96

* Each value represents the average of three animals.

† The net absorbed dose was taken as the amount of activity found in the tissues plus that excreted in the urine, allowing no excretion of absorbed material via the gastrointestinal tract.

TABLE 3.—*Gross Distribution of C^{14} Activity in Terms of Per Cent of Administered Dose at Various Times after Oral Administration of C^{14}-DEA to Rats.*

Distribution of Administered Dose	Time After Oral Administration*				Average Values
	6 Hr.	12 Hr.	24 Hr.	36 Hr.	
Net Absorption,† % Administered Dose	23.14	44.57	20.97	21.27	27.49
G.I. Tract & Contents, % Administered Dose	77.70	52.78	45.07	18.16	48.43
Feces (Excreted), % Administered Dose	0.14	0.04	35.38	57.04	23.15
Total Recovery, % Administered Dose	100.98	97.39	101.42	96.47	99.07

* Each value represents the average of three animals.

† The net absorbed dose was taken as the amount of activity found in the tissues plus that excreted in the urine and as CO_2, allowing no excretion of absorbed activity via the gastrointestinal tract.

(formula II). Only about 3.6 per cent of the net absorbed activity was exhaled as carbon dioxide in 36 hours which was equivalent to 7 per cent of the C^{14} activity present in the carbethoxy group alone. As decarboxylation of organic acids is a rather common occurrence in biologic systems it seems reasonable to assume that the carboxyl group was the source of the $C^{14}O_2$ rather than the carbon atom in the methylene bridge.

TABLE 4.—*Distribution of Activity in Terms of Per Cent of Net Absorbed* Dose Per Organ at Various Times after Oral Administration of C^{14}-Dicumarol and DEA to Rats.*

Tissue or Excreta	Time in Hours after Oral Administration†								
	Dicumarol					DEA			
	6	12	24	36	48	6	12	24	36
Liver	14.38	11.71	6.57	4.97	4.89	19.23	6.08	4.83	3.94
Blood	18.38	15.04	7.77	5.52	1.75	15.00	7.53	4.70	4.32
Kidneys	1.97	1.98	1.11	0.92	0.91	2.43	1.28	0.57	0.30
Heart	0.46	0.47	0.15	0.10	0.15	0.32	0.17	0.10	0.11
Lungs	1.36	1.10	0.37	0.24	0.15	0.90	0.51	0.23	0.17
Skin and Hair	24.02	17.89	8.52	7.94	11.69	17.38	8.50	7.98	5.62
Remains	37.43	31.76	13.18‡	10.74	10.11	29.66	13.09	10.25	15.30
Urine	2.00	20.05	62.33	69.57	70.35	14.55	61.40	68.76	66.64
CO_2	0	0	0	—	—	0.53	1.44	2.58	3.60§

* Net absorbed dose was taken as the amount of radioactivity found in the tissues plus that excreted in the urine and as CO_2, allowing no excretion of absorbed material via the gastrointestinal tract.

† Each value represents the average on three animals.

‡ Of this fraction, the testes accounted for 0.26%; the spleen, .06%; the thymus, .07%; and the brain, .03% of the total absorbed dose.

§ 36 hour value for CO_2 not measured but estimated for the purpose of calculating the other results at 36 hours.

TABLE 5.—*Distribution of Activity in Terms of Per Cent of Net Absorbed* Dose Per Gram of Wet Tissue at Various Times after Oral Administration of C^{14}-Dicumarol and DEA to Rats.*

Tissue or Excreta	Time in Hours after Oral Administration†								
	Dicumarol					DEA			
	6	12	24	36	48	6	12	24	36
Liver	1.60	1.42	0.56	0.40	0.38	2.02	0.69	0.53	0.34
Blood‡	1.32	1.14	0.53	0.35	0.11	1.09	0.61	0.34	0.32
Kidneys	1.08	1.16	0.59	0.48	0.43	1.31	0.76	0.32	0.19
Heart	0.60	0.57	0.19	0.12	0.18	0.44	0.21	0.13	0.15
Lungs	1.04	0.79	0.29	0.18	0.12	0.73	0.40	0.19	0.16
Skin and Hair	0.63	0.54	0.23	0.21	0.33	0.48	0.28	0.23	0.17
Remains	0.31	0.28	0.11§	0.09	0.09	0.25	0.12	0.08	0.13
CO_2	0	0	0	—	—	0.19	0.25	0.23	0.21

* Net absorbed dose was taken as the amount of radioactivity found in the tissues plus that excreted in the urine, allowing no excretion of absorbed material via the gastrointestinal tract.

† Each value represents the average on three animals.

‡ Values for other tissues incorporated into the remains but analyzed separately are: bone marrow, 0.21%; testes, 0.11%; spleen, 0.11%; muscle, 0.11%, thymus, 0.10 %; bone, 0.09%; and brain, 0.02% of net absorbed dose per gram.

§ The values for blood are given as per cent of absorbed dose per cc.

Filter paper partition chromatographic analyses of the urines and plasmas of animals treated orally with C^{14}-labeled dicumarol and C^{14}-labeled DEA indicated (but did not con-

clusively prove) that unchanged dicumarol and DEA were present in appreciable amounts in both plasma and urine (fig. 3). The chromatographic analyses also indicated that there may be as many as seven metabolites of dicumarol and three of DEA present in the urinary excretion.

A comparison of the studies given in this report with those reported recently by Lee and co-workers[8] of the metabolism of C^{14}-dicumarol following intravenous administration to mice and rabbits indicates an appreciable difference in the mode of metabolism of dicumarinyl derivatives following intravenous and oral administration.

Summary

1. Clinical observations in normal subjects and in patients suffering from thromboembolic diseases showed that 4,4′-dihydroxydicumarinyl ethyl acetate (Pelentan, Tromexan) has a quicker, more transient hypoprothrombinemic effect and less apparent side effects than does dicumarol. The quicker, more transient action of the former substance may provide an advantage over dicumarol for the control of thromboembolic diseases.

2. Animal experiments with C^{14}-labeled dicumarol and 4,4′-dihydroxydicumarinyl ethyl acetate indicated that the quicker, more transient action of the latter substance is associated with a more rapid drop in body retention, paralled by a higher urinary excretion rate in the first few hours following oral administration. In general, the slower rate of metabolic turnover of C^{14} activity following administration of labeled dicumarol may be responsible for its prolonged hypoprothrombinemic effect.

3. The experiments indicated that the mode of action of the two substances is essentially the same. Maximal absorption and the maximal concentration of the radioactivity occurred within six hours after oral administration. The time of maximal absorption and maximal tissue radioactivity was not positively correlated with the time of maximal hypoprothrombinemic effect. In the case of DEA, however, there seemed to be a higher initial liver concentration and an earlier drop in the percentage of retained activity in the tissues of the animal, paralleled by a higher urinary excretion rate immediately following administration.

4. Filter paper partition chromatographic analysis suggested the presence of unchanged dicumarol and unchanged DEA both in the urine and the plasma of animals treated orally with the radioactive materials. The analyses suggested the possible production of seven metabolites in the case of dicumarol and at least three in the case of 4,4′-dihydroxydicumarinyl ethyl acetate.

5. Preliminary studies following intravenous injection of the labeled materials suggested an appreciable difference in the mode of metabolism of dicumarinyl derivatives following oral and intravenous administration.

Acknowledgements

The authors wish to express their appreciation to Dr. A. R. Ronzio, Mr. Arthur Murray, III, and Mr. Wayne Bills who synthesized the labeled compounds, and to Miss Edith Heidlebaugh of the Los Alamos Medical Center for technical assistance.

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Spatial Vector Electrocardiography

The Clinical Characteristics of S-T and T Vectors

By Robert P. Grant, M.D., E. Harvey Estes, Jr. M.D., and Joseph T. Doyle, M.D.

The application of a spatial vector method of interpretation to the S-T and T deflections in the conventional electrocardiogram is described, and the vector abnormalities responsible for the more commonly encountered deformities are discussed. In addition, the isolated T-negativity syndrome is described, a rare type of precordial T-wave inversion which may be encountered in normal subjects and is often indistinguishable from the ST-T deformity of recent myocardial infarction. The spatial vector method of interpretation is found to provide a simple yet rational basis for the interpretation of these often bizarre wave forms.

IN THE PAST, the clinical interpretation of the S-T segment and the T wave in the electrocardiogram has been based upon the size and direction of the deflections in individual leads. With the development of multiple precordial leads and unipolar limb leads, this method of interpreting ST-T contours has become more and more difficult and arbitrary. Recently it has been shown that, in the human subject, all body surface deflections can be treated as, in effect, recordings from the same central resultant electrical forces or vectors.[1] This means that, by and large, the deflections are different on the various leads in a given patient because each lead records a different projection of essentially the same vectors. It is possible to determine the characteristics of these central resultant vectors from the deflections on the conventional leads and the interpretation of the electrocardiogram can be based upon these data. Such a method for interpretation simplifies clinical electrocardiography because it makes it possible to express the many different contours and amplitudes of QRS and T deflection on the various leads in a given patient in terms of the spatial directions of the responsible vectors. In addition, it is a more objective and rational method of interpretation than methods based upon deflection "patterns" in individual leads.

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Aided by a grant from the Life Insurance Medical Research Fund.

In a previous paper, a method was described for determining the direction in three dimensional space of instantaneous and mean vectors from simple inspection of conventional limb and precordial leads, and the characteristics of normal and abnormal spatial QRS vectors were presented.[2] In the present paper the S-T and T vectors will be discussed with particular reference to the way in which precordial ST-T abnormalities are produced. The material will be presented descriptively with little discussion of the bioelectric abnormalities responsible for these deformities. However, the spatial vector method has made it possible to apply objective and semiquantitative technics to the study of the mechanisms of S-T and T abnormalities in the human subject, and this material will be presented elsewhere.

Material and Methods

The cases were obtained from 3000 consecutive clinical electrocardiograms taken at the Grady Memorial Hospital. In all cases, the three standard limb leads and six precordial V leads had been taken. In many subjects unaugmented unipolar extremity leads were also available. In certain subjects the projection of T forces on the chest surface was studied by recording unipolar V leads at two inch intervals along a series of vertical lines from above the clavicles to the umbilicus.

The method for study was the spatial vector method described in detail previously.[2] In brief, the frontal plane projection of the mean spatial vector is determined from the three limb leads on a triaxial reference figure. Then, the spatial direction of this mean vector is determined by identifying the precordial electrode position where a transitional deflection was recorded from that vector. These two

data make it possible to plot the transitional pathway for the vector, which is the line around the chest where a plane perpendicular to the vector would intersect the body surface. Plotting the transitional pathway makes graphic the direction of the responsible vector and indicates the distribution of positive (upright) and negative (inverted) deflections on the chest for that vector.

The S-T and T contours are recordings of the variations in magnitude and direction of resultant vectors from one instant to another during a single ST-T cycle. When these instantaneous vectors are translated to the point of relative zero in a drawing of the electrical field of the heart, they define an ellipse which is called the spatial ST-T loop or vectorcardiogram. The method for constructing the ST-T loop from conventional leads is the same as that for calculating the QRS loop and has been described previously.[2]

It will be recognized that this method for studying the electrical field of the heart treats the body as if it were a regular cylindric volume conductor of relatively homogeneous conductive properties with the heart at its center. Accordingly, variations in the contour of the chest and in the eccentric position of the heart as well as variations of the placement of the precordial electrode will be sources of error in the calculations of spatial vectors by this method. Such errors are, however, rarely large enough to significantly influence the interpretation or impair the validity of the method for clinical purposes. It must be remembered that body surface deflections give at best only a vague and general notion of the electrical forces of the heart, no matter how accurate the recording instrument, or how precise or elaborate the method for interpreting them.

Space will not permit a discussion of secondary T wave abnormalities. These are the T wave changes which accompany ventricular conduction disturbances and can be expected whenever the QRS interval exceeds 0.12 to 0.14 second. However, vector methods are applicable to these disorders, and, indeed, by the spatial vector method of interpretation it is possible to detect primary T-wave abnormalities when they are superimposed on the secondary T-wave changes.

In the illustrations, the three standard limb leads and precordial leads V_1 to V_6 are shown. Below the tracings, frontal and coronal plane ST-T loops and mean QRS vectors are drawn; and the mean spatial QRS, S-T and T vectors are shown three-dimensionally with drawings of the transitional pathways on the chest for the mean spatial S-T and T vectors for each subject. To be sure, the coronal plane loop is not entirely accurate in these drawings because the V_1 to V_6 electrode positions from which the coronal projection of the loop is constructed do not all lie in the same coronal plane of the body. Furthermore, in order to make the illustrations as simple and legible as possible, complete accuracy in drawing the loop and plotting the directions of the spatial vectors had to be sacrificed in certain instances. However, these inaccuracies are slight and do not interfere with the general validity of the reconstructions. Finally, in some illustrations, the QRS complexes were retouched, but in no instances were ST-T waves retouched.

Results

From a descriptive point of view, three vector abnormalities account for nearly all the variations in ST-T contours which are encountered in limb and precordial leads. They are (1) abnormalities in the direction of the mean spatial T vector, accounting for variations in the distribution of positive, negative, and transitional T waves among the various leads, (2) abnormalities in the contour of the ST-T loop, accounting for abnormal S-T segments in these leads, and (3) apparently extracardiac factors which locally affect the propagation of T forces, as is seen in what is called the isolated T-negativity syndrome. They will be discussed in that order.

1. *The Direction of the Mean Spatial T Vector*

In a given subject, the mean spatial T vector in effect divides the body surface in half, as far as the type of T wave recorded from various regions of the body surface is concerned. One half, the half toward which the vector is pointing, is an area of resultant electrical positivity, and unipolar electrodes placed anywhere on this region will record positive or upright T waves. The half of the body surface away from which the vector is pointing is the area of resultant electrical negativity, and negative or inverted T waves are recorded by unipolar electrodes placed in this region. The two areas are separated by the transitional pathway which is the line of intersection on the body surface of a plane perpendicular to the vector. Electrodes placed on the transitional pathway will record isoelectric T waves, or T waves with as much positivity as negativity. Accordingly, the most rational way to interpret the T waves recorded in the various leads of a given electrocardiogram is to determine from them the direction of the mean spatial T vector for that subject and base the interpretation on this information.

The simplest of rational methods for defining normal and abnormal directions of the mean spatial T vector is to evaluate the angle it makes with the mean spatial QRS vector in the given subject, and compare this with established criteria of normal and abnormal QRS-T angles. There are several reasons for using this as the basis of the clinical interpretation. First, it is easy to do, requiring no special equipment. With a little experience, the spatial QRS-T angle can be calculated from inspection of the limb and precordial leads in no more time than it takes to interpret the tracing by any other method. Second, the direction of the mean spatial QRS vector is altered by relatively few intracardiac conditions[2] while, as will be seen, the direction of the mean spatial T vector is influenced by a host of different subtle physiologic and pathologic conditions. Accordingly, the direction of the QRS vector provides a relatively stable reference datum for the evaluation of the direction of the T vector. Third, as Wilson and his colleagues have shown, there is a fundamental electrical relationship between the manifest QRS forces and manifest T forces in a given individual and this relationship when expressed quantitatively is called the ventricular gradient for that subject.[3] The abnormal electrocardiogram represents a disturbance in this relationship, and the location and intensity of the disturbance is manifested by a relatively specific change in the magnitude and direction of the T vector as compared with the QRS vector. Accordingly, the QRS-T angle is a property of the ventricular gradient and its use brings the rational and objective aspects of the ventricular gradient concept to routine clinical interpretation. Fourth, a change in the location of the heart in the chest will alter QRS and T deflections in all leads; however, it will not influence the QRS-T angle, provided the myocardium has remained unchanged. This is useful in the interpretation of follow-up tracings because it helps to differentiate changes in the QRS and T waves which are due to alterations in the position of the heart in the chest from those which are due to intrinsic myocardial abnormalities.

In the vast majority of normal subjects, the mean spatial QRS vector tends to be directed leftward, inferiorly, and somewhat posteriorly to the frontal plane of the body. In young subjects it tends to point relatively vertically, while in older subjects it tends to have a more horizontal direction.[2] Normally the mean spatial T vector tends to be relatively parallel with the mean spatial QRS vector. Usually the spatial QRS-T angle is less than 40° and only infrequently does it exceed 50° in normal subjects. Its precise relationship to the QRS vector varies somewhat with age and body build. In young subjects, it is directed somewhat posteriorly to the frontal plane and the transitional T wave is therefore commonly encountered at electrode position V_3 or V_4. Occasionally this juvenile pattern persists into the third decade. In older age groups, the T vector gradually rotates anteriorly and rightward so that V_2 or V_1 or even electrode positions to the right of V_1 write the transitional T wave. These variations are illustrated in figure 1*D*.

The variations in the direction of the T vector with age are no doubt related to hemodynamic and structural differences between right and left ventricle in these age groups. The T process takes place during ventricular systole, and the magnitude and direction of the mean T force therefore varies with the systolic sizes, wall thicknesses and intramyocardial pressures of the two ventricles. In young subjects, the right ventricle is relatively dominant and the T vector tends therefore to point somewhat away from the location of the right ventricle in the chest. In adults, on the other hand, the left ventricle is relatively dominant and the T vector tends to point more or less away from its location in the chest.

In older age groups another process appears which is believed to alter repolarization. This is myocardial ischemia, secondary to the coronary vascular changes which occur in nearly all older subjects. Myocardial ischemia delays repolarization, causing the T vector to point away from the affected region.[4] Since in general these coronary vascular changes affect the left ventricular myocardium more than the right, the T vector tends to point away from the location of the left ventricle in the chest in these subjects. The QRS vector is relatively unaltered by ischemia and accordingly QRS-T

angles over 60° are not uncommon in this older age group with little or no other evidence of myocardial disease. The wide QRS-T angle of left ventricular ischemia is probably the commonest abnormality of the ventricular complexes encountered in clinical electrocardiography. It is well to remember, however, that the electrical evidence of ischemia precedes comes to lie in the area of relative T positivity and the transitional T pathway approaches the midaxillary line (fig. 1*D*). This accounts for the frequency of low or inverted T waves in lead V_6 in this syndrome. However, in the course of the development of left ventricular ischemia the direction of rotation of the T vector depends upon the electrical position of

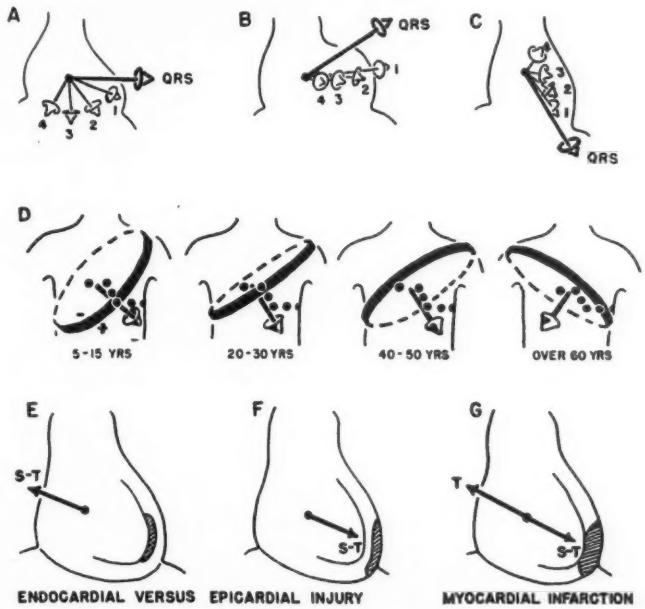

FIG. 1. *A, B, C*: The changes in direction of the mean spatial T vector as left ventricular ischemia develops. Three electrical positions of the heart are shown: *A*, horizontal, *B*, leftward, and *C*, vertical.

D: The distribution of positive and negative T waves on the body surface at various age groups. The black band indicates the distribution of transitional deflections for the given T-vector direction, and the black dots represent the standard precordial lead electrode positions.

E, F: The relationship between the effective location of myocardial electrical "injury" and the direction of the S-T vector.

G: The relationship between the directions of the S-T and T vectors and the effective location of a myocardial infarction.

actual histologic evidence of myocardial damage, and the clinical implications of this electrocardiographic abnormality in a given case therefore will usually depend upon other clinical findings.

In the electrocardiographic syndrome of left ventricular ischemia, the T vector usually comes to be more and more anteriorly directed, pointing away from the left ventricle. Accordingly, more and more of the anterior chest the heart. When the heart is in intermediate electrical position, as indicated by the direction of the QRS vector, the T vector usually rotates anteriorly and rightward producing a low or inverted T_1 while T_2 and T_3 remain upright (fig. 1*A*). When the heart is in horizontal electrical position, the T vector tends to rotate nearly directly anteriorly, causing the frontal plane projection of the T vector to become smaller without change in direction so that the

limb lead T waves become small in amplitude but remain upright (fig. 1*B*). When the heart is in a vertical electrical position, the T vector tends to rotate anteriorly and slightly leftward, causing inversion of T_2 and T_3 while T_1 remains upright (fig. 1*C*).

As far as the T loop in the normal subject is concerned, cathode tube vectorcardiograms show it to be a nearly straight line; that is, the various instantaneous vectors which write the T wave are relatively parallel with one another in a given normal subject. However, because the instantaneous vectors are not entirely parallel with one another, their difference in direction will cause some to project small positive components and others to project small negative components on the axis of a lead taken in the transitional pathway. This is the explanation for the bizarre, multiphasic T waves frequently recorded from the transitional pathway in normal subjects. The deflections at V_2 and V_3 in figure 2*A*, obtained from a subject with no evidence of heart disease, illustrate this. Here, the instantaneous T vectors are directed first anteriorly, then posteriorly, then anteriorly to the vector which is perpendicular to the transitional plane. That the variations in direction of instantaneous T vectors responsible for the bizarre T waves are actually very slight can be seen in the coronal plane drawing of the ST-T loop for this subject. Accordingly, with present knowledge of T forces, these are normal ST-T waves.

The reason for the different directions of the instantaneous T vectors in the normal subject is not known. The variation in direction is extremely slight, for the bizarre transitional T waves are recorded from only a narrow region in the transitional pathway. Indeed, in many subjects this region is so narrow that it passes between two precordial electrode positions and the multiphasic wave forms are not seen in the routine tracing. However, careful exploration of the transitional region in such subjects will usually demonstrate the multiphasic complexes. Occasionally, this pathway runs through the electrode position of one or another limb lead in which case the bizarre T wave will be recorded in the limb leads, as in leads II and III of figure 2*B*. The bizarre contour is not usually as striking in these leads, however, because the amplitude of the various components of the electrocardiogram is much smaller in more remote leads.

As the ST-T loop becomes wider, the pathway of multiphasic transitional complexes forms a broader band around the chest so that more and more precordial electrode positions are included in the transitional pathway. Such loops are abnormal and will be discussed in greater detail in the next section. However, it is important to recognize that the occurrence of the bizarre complex at more than one precordial electrode position may be due to the unusual direction of the mean spatial T vector and not to an abnormal loop. For example, when the T vector has such a direction that its transitional pathway runs through two or more precordial electrode positions, each of these leads may show multiphasic T waves. This is exemplified in figure 2*C*, obtained from a normal subject. Here the transitional pathway runs through V_2, V_3, and V_4 electrode positions causing three of the six V leads to record bizarre transitional complexes, although, as can be seen in the drawings, the difference in direction of successive vectors is quite slight and the ST-T loop cannot be differentiated from the normal.

When the mean spatial T vector has an abnormal direction, the transitional T wave is, of course, recorded at different precordial electrode positions. For example, with left ventricular ischemia, the bizarre transitional T waves may be recorded at V_5 or V_6 instead of V_1 or V_2 as in the normal subject.

It is important to realize that when the transitional T pathway runs near or through one or another precordial electrode position, slight differences in the placement of that electrode in follow-up tracings will result in definite changes in the contour of the T wave it records. In left ventricular ischemia, for example, a difference in the location of the V_6 electrode of only a few centimeters may change it from lying in the area of relative positivity and writing an erect T wave to lying in the area of relative negativity where an inverted T wave will be written. Similarly, slight variations in the position of the heart in the chest or differences in the re-

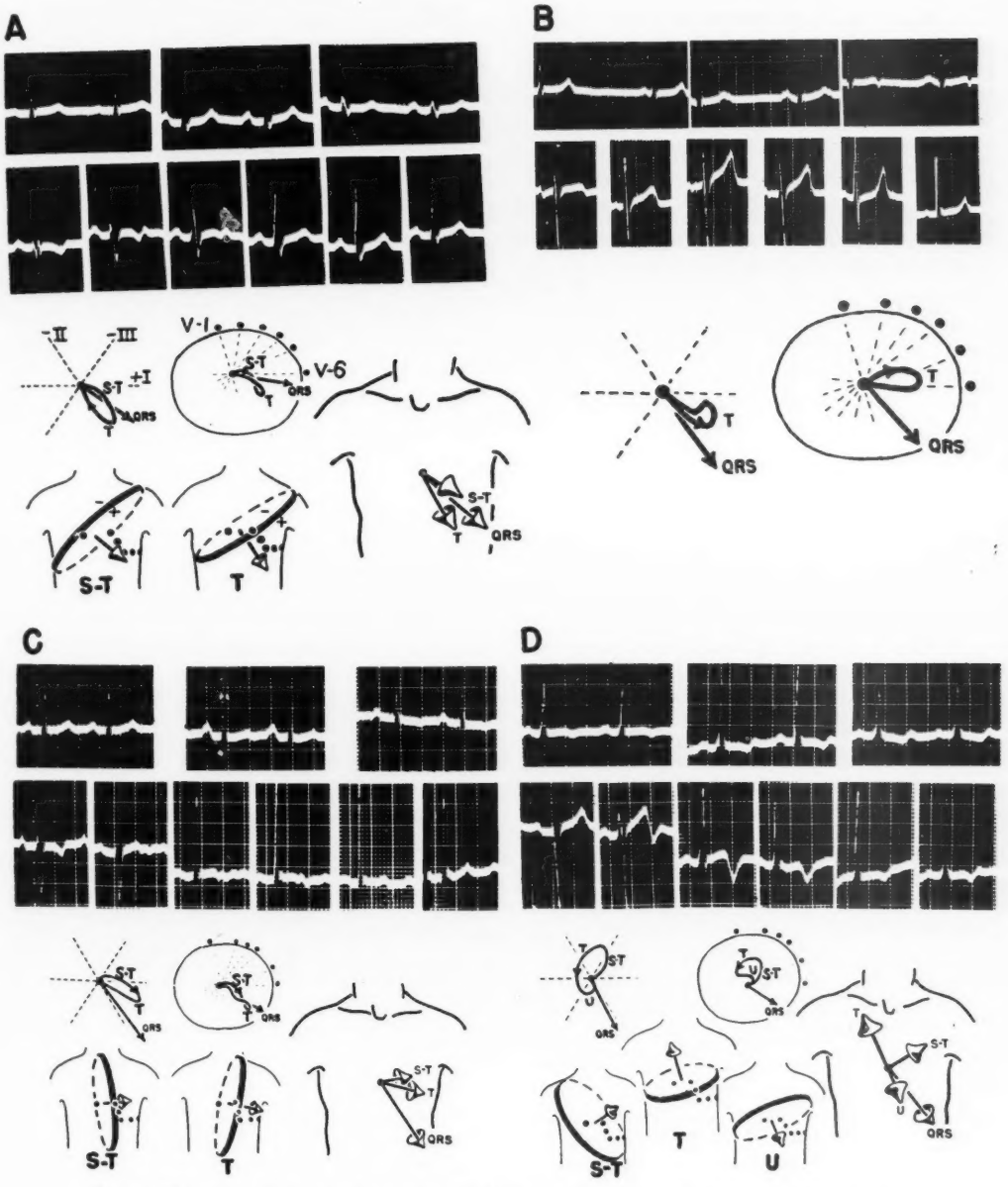

FIG. 2. This figure illustrates how minor variations in the direction of successive instantaneous ST-T vectors account for bizarre precordial ST-T segments, discussed more fully in the text. Frontal and coronal plane projections of the ST-T loop, transitional pathways, and spatial directions of mean vectors for portions of the loop are shown.

cumbent position of the patient in serial tracings will change the location of the transitional pathway on the chest so that the T waves recorded from a region of the chest near this pathway may be positive one time and negative the next.

There is only one other commonly encountered cause of abnormal direction of the T vector in addition to ischemia. This is ventricular hypertension, causing what is perhaps inappropriately called the ventricular strain syndrome. From an electrocardiographic point of view it is probably justified to distinguish between the T vector abnormalities of "ischemia" and "strain." In the first place, there is reason to believe that the bioelectric disturbance responsible for each is different; that is, while the ischemia abnormality can apparently be correlated with actual vascular insufficiency in most instances, the strain abnormality appears to be in large measure due to a direct effect on excitation of increased myocardial membrane tension. In the second place, the ischemia abnormality frequently represents a relatively localized disturbance of repolarization in the left ventricle with the T vector pointing away from the affected region; accordingly, the QRS-T angle is not commonly over 120°. In the strain syndrome, on the other hand, the T vector abnormality appears to be a result of altered repolarization throughout an hypertrophied ventricle. Accordingly, in addition to the QRS vector being increased in magnitude and altered in direction, the T vector is nearly completely opposite to it in direction; that is, the QRS-T angle is from 150° to 180° (fig. 3*C*).

These two processes, ischemia and strain, appear to account for nearly all abnormalities in the direction of the T vector clinically. It is nearly certain, however, that with further study of the mechanisms of T vector abnormalities, many abnormalities at present indistinguishable from ischemia effects and currently so designated will be found to be due to other subtle disorders. Similarly, intramyocardial pressure variations analogous to those seen in the strain syndrome but not as severe and not accompanied by hypertrophy can cause transient abnormalities of T vectors, and are no doubt responsible for many of the so-called functional abnormalities of T waves. Accordingly, it is perhaps wisest to consider the electrocardiographic diagnoses of "ischemia" and "strain" as strictly electrical terms, and their clinical implications in a given case as dependent upon other clinical data.

2. *The S-T Vector and Abnormalities of the ST-T Loop*

The portion of the electrical cycle of the heart which follows the QRS complex is made up of instantaneous resultant spatial vectors which are believed to represent, with extremely rare exceptions, solely electrical forces of repolarization. In the normal subject, there is relative quiescence of this process in the immediately post-QRS interval. The electrocardiogram shows little deviation during this period and it is descriptively called the S-T interval. Later in the post-QRS period, the repolarization forces swell in magnitude, writing what is descriptively called that T wave. Frequently, however, repolarization forces of measurable magnitude appear during the S-T interval and they may have different directions from the forces during the T interval. Accordingly, it is convenient to treat the electrical events in the post-QRS period in terms of a mean spatial T vector and a mean spatial S-T vector. In this sense, the mean S-T vector is the vector sum of the forces preceding the T wave, whether or not there is also a shift of J. Although this may one day prove to be an oversimplification of post-QRS forces, at the present time the vast majority of abnormalities of the ST-T segment encountered in clinical electrocardiography can be accounted for by variations in the directions of these two mean spatial vectors.

When the ST-T loop is abnormal in contour, the transition from the direction of the vectors during the S-T interval to their direction during the T interval tends to be gradual and orderly. This is important in clinical electrocardiography because, with a wide loop, the peak of the T wave will not be written at the same time after the onset of QRS complex in all leads. The reason for this is that the portion of the ST-T loop which accounts for the maximum projection of ST-T vectors on the axis of one lead is not the same portion which accounts for the maximal projection on the axis of another lead, and the two portions represent

different instants in the time course of the ST-T loop. This explains why the Q-T time may lead, late on another, and be bowed or curved on a third. In figure 2*D*, for example, what

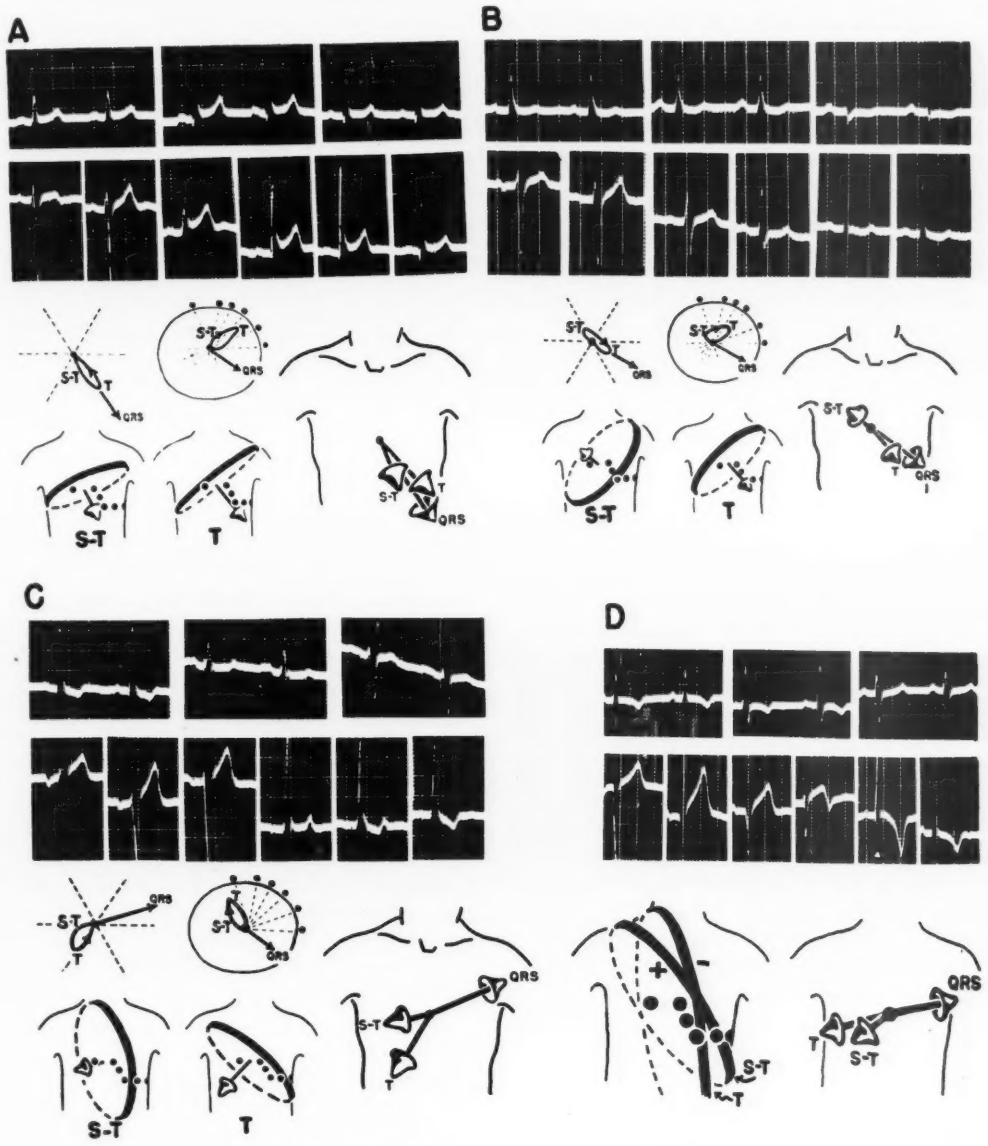

FIG. 3. Similar to figure 2. See text for discussion.

be different on various leads in a given subject, and why the S-T segment may show its maximum deviation early in the S-T interval on one would be called T wave in V_1 coincides in time with the last part of the S-T segment in V_6, and the bizarre, deep negative portion of the T

wave in V_2 coincides with an isoelectric interval between ST-T forces and what would be called a U wave on leads II and III of the same subject. Obviously, to designate an S-T segment, T wave or U wave in the individual leads in this case would be difficult and arbitrary. However, the electrical abnormality responsible for these contours can be easily understood when the ST-T loop is drawn, and the interpretation can be based upon the mean directions of S-T, T, and U vectors.

Since the S-T period is normally a period during which the repolarization forces are gradually increasing in magnitude it should not be surprising that occasionally normal subjects will show significant deviations of S-T segments simply because of an over-all increase in the magnitude of repolarization vectors. Indeed, S-T displacement due to normal repolarization during the S-T interval is regularly seen at V_2 and V_3 in normal subjects because the proximity of these electrodes to the heart results in a relative magnification of all cardiac electrical forces in the recorded deflection. However, in young adults the repolarization vectors are often unusually large in magnitude, producing large T waves and measurable S-T segment deviation in the limb as well as the precordial leads. Under these circumstances the spatial S-T vector is relatively parallel with the spatial T vector. Figure 3*A* illustrates such a case. This was obtained from a young student nurse who had no evidence of cardiovascular disease. The striking elevation of the S-T segment at V_3 to V_6 persisted for over a year without change.

The cause of this increase in magnitude of normally directed repolarization vectors in the young adult is not known. However, because the mean T vector is a resultant of repolarization forces from all regions of the ventricular myocardium, in these cases there must be an alteration in repolarization of roughly the same intensity and duration of all regions of the heart. This would suggest that systemic or general metabolic factors are responsible rather than local myocardial or hemodynamic factors. Indeed a change in the magnitude of the T vector without a change in its direction may be seen in a host of systemic physiologic and pathologic conditions: after meals, during exercise, during sleep, in the presence of anemia. anoxia, acidosis, in hyperthyroidism and hypothyroidism, beri-beri, hyperpotassemia and other conditions. On the other hand, when the repolarization processes are altered asymmetrically in the heart, the mean spatial T vector is changed in direction, tending to point away from the affected region. In the vast majority of clinically manifest forms of heart disease there is an asymmetric hemodynamic or structural alteration in the heart, and the T vector therefore becomes abnormally directed, with or without a change in its magnitude. Indeed, it was largely because there is a change in direction of the T vector in most clinical heart diseases that the electrocardiogram came to have its great clinical differential diagnostic value.

Occasionally, the S-T vector due to normal early repolarization forces is difficult to distinguish from the S-T vector due to acute pericarditis. The reason for this is that in pericarditis the cell injury results in a dissipation of repolarization forces in such a way that S-T segment deviations appear, representing an S-T vector which points toward the center of the injured region. In pericarditis the center of the injured region is usually the apex of the heart. Accordingly, the S-T vector in this disorder has a direction which is relatively parallel with the normal T vector, resembling the situation in the subject with normal early repolarization. Often not until pericardial ischemic changes appear, causing the T vector to have an abnormal direction, can the two causes of S-T deviation be differentiated. Of additional help in differentiating them is the fact that the S-T vector is transient in pericarditis, lasting only a week or so, and the T vector is not increased in magnitude. On the other hand, in the subject with normal S-T deviation, the S-T vector persists for years and the T vector is always unusually large in magnitude.

When the spatial T vector is abnormal in direction and increased in magnitude, there will be an S-T vector due to early repolarization forces which is relatively parallel with this abnormally directed T vector. In general, such an S-T vector is not seen in the electrocardio-

gram of uncomplicated ventricular ischemia but is characteristically seen in the ventricular strain syndrome (fig. 3*C*). In these latter cases, the S-T vector usually is not perfectly parallel with the T vector and therefore the S-T and T transitional pathways do not coincide on the chest surface. Because of this, there are usually small regions of the chest where S-T elevation with T inversion or vice versa may be recorded while elsewhere the S-T and T deviations are concordant. In the individual tracings, the discordant patterns may sometimes closely resemble the ST-T deformity of myocardial infarction, as can be seen at V_4 in figure 3*D*. This tracing was obtained from a 43 year old man with aortic insufficiency due to rheumatic fever, but with no clinical evidence of coronary artery disease; the tracing showed no change during 18 months of observation. When vector methods are used there is rarely any difficulty in distinguishing the two causes of S-T and T discordancy, regardless of what an individual deflection looks like, for in myocardial infarction the S-T and T vectors are nearly completely opposite in direction (fig. 1*G*), while in the strain pattern they are relatively parallel with one another.

Most abnormal ST-T wave forms, and therefore most abnormal ST-T loops, can be represented by differences in the directions of just two vectors, a mean spatial S-T vector and a mean spatial T vector. When studied in this light, it is found that two clinical circumstances account for the great majority of instances where the two vectors have significantly different directions. These are (1) digitalis administration, and (2) injury current. Among less common causes of differences in the directions of the two vectors are marked tachycardia and hyperkalemia, and these are usually easily rec-

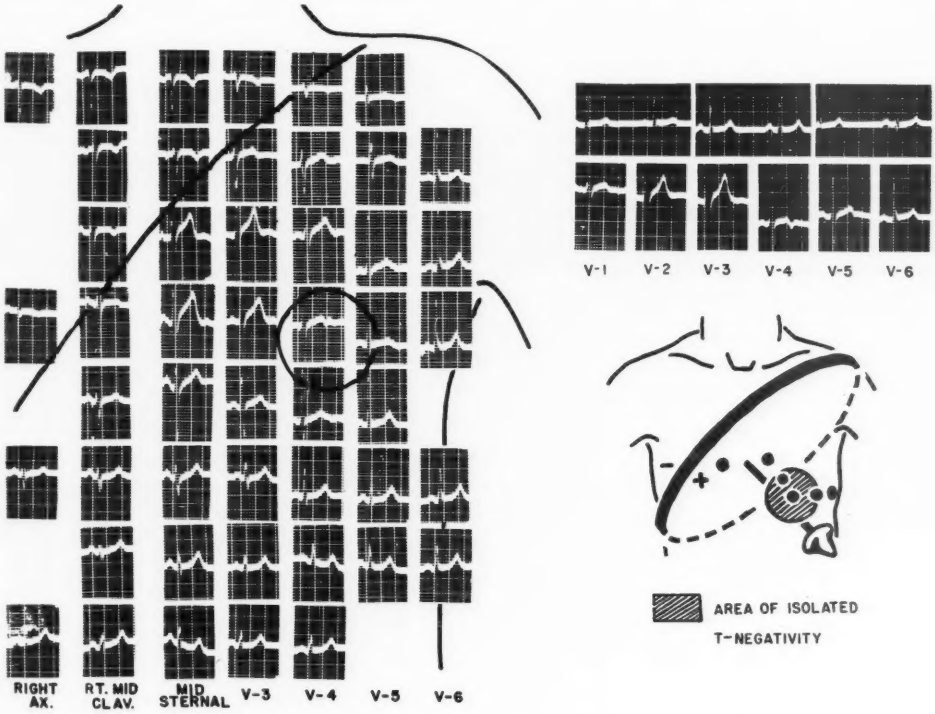

FIG. 4. A healthy young adult with an abnormal T wave at V_4. Extensive explorations of the chest show that the T deformity is localized and is inconsistent in location with the direction of the spatial T vector.

ognized on other grounds. Undoubtedly, with further research, other factors which influence the directions of forces during the ST-T interval will come to light and require modification of these generalizations. In the present discussion the electrocardiographic effects of digitalis administration and injury current will be considered.

In brief, following digitalis administration, the entire repolarization process is accelerated so that the majority of repolarization vectors are generated during the S-T interval and the Q-T interval is measurably shortened. In addition, there is an alteration in fiber energetics during systole in both the normal and abnormal subject which causes the accelerated repolarization forces to be different in direction from those generated during the T interval. Accordingly, following digitalis administration, the mean S-T vector comes to be directed nearly 180° from the direction of the mean QRS vector, while the mean T vector remains unchanged in direction, gradually dwindling in magnitude as the S-T vector becomes larger and larger at each stage of digitalization. This is illustrated in figure 3*B*, obtained from a normal subject after digitalization. It will be noted that the QRS-T angle is normal and the S-T vector is about 160° from the QRS vector in space.

The fact that the T vector is unchanged in direction following digitalis administration, other factors remaining the same, is of importance in clinical electrocardiography, for it means that an abnormal T vector can be recognized whether or not digitalis effects are present in the electrocardiogram. Thus, for example, the wide QRS-T angle and rightward and anteriorly directed T vector of left ventricular ischemia can be recognized even when digitalis effects are present as manifested by an S-T vector relatively opposite in direction to the QRS vector.

When digitalis is given in the presence of the ventricular strain syndrome, the Q-T interval is shortened without change in the ST-T contours, presumably because the repolarization forces are already rotated nearly 180 degrees from the direction of the mean QRS vector (fig. 3*C*). Accordingly, digitalis effects cannot usually be detected in the presence of the strain pattern. When amounts of digitalis are given which are too small to produce characteristic electrocardiographic alterations slight hemodynamic alteration in the heart may result in the pattern of complete digitalization. For example, simple breath-holding in full inspiration in a subject who has received digitalis will cause an S-T vector to appear, opposite in direction from the mean QRS vector, and will cause the T vector nearly to vanish. For this reason it is difficult to evaluate the degree of digitalization in a given subject from the degree of electrocardiographic change. The mechanism whereby digitalis brings about these electrocardiographic changes and their relationship to the mechanical properties of the heart will be discussed in greater detail in a later paper.

The second cause of abnormally directed S-T forces is "injury current," which represents a steady-state electrical force resulting from actual cell membrane injury.[5] Without going into details of its mechanism, the injury current acts as an electrical "leak" during the period that the myocardium is polarized and is effectively absent when the myocardium is depolarized. Accordingly, it produces an apparent S-T segment deviation which can conveniently be represented by an S-T vector. The magnitude of the S-T vector depends upon the size of the injured region and the intensity of injury, and its direction depends upon the location of the injured region of the myocardium. Thus, when the injury is in epicardial layers, as in pericarditis and classical myocardial infarction, the S-T vector tends to point toward the affected region of the ventricle (fig. 1*E*). When the injury is more endocardial in location, as in angina pectoris, coronary insufficiency, and subendocardial infarction, the S-T vector in general points away from the affected region (fig. 1*F*).[6]

When an "injured" epicardial region is also ischemic, as is often the case, the ischemia causes the T vector to point away from this region, as was described earlier. Under this circumstance, the S-T and T vectors are oppositely directed, and this explains the discordant S-T and T contours seen in myocardial infarc-

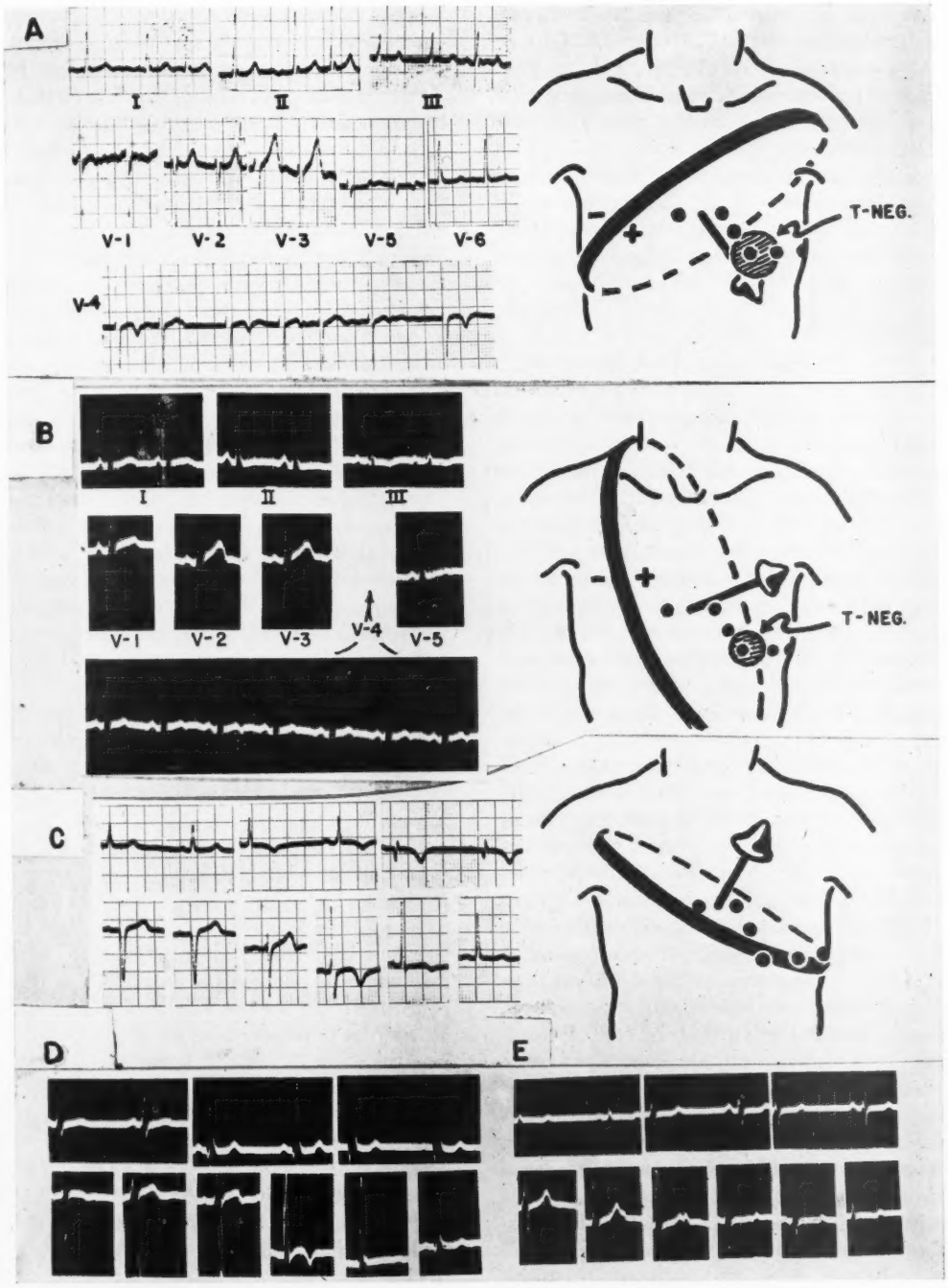

FIG. 5. Illustrating other aspects of isolated T negativity.

tion and the "coving" of the ST-T segment during recovery (fig. 1*G*). However, in the very early stages of myocardial infarction, the S-T and T vectors are often relatively parallel, both greatly increased in magnitude and both pointing toward the infarcted region. Perhaps this "against the rule" behavior of the T vector is due to an intense subendocardial ischemia at the onset of the infarction, for this would cause the T vector to point *toward* the affected region.[7]

3. *Isolated T Negativity*

In the course of the survey of 3000 consecutive clinical electrocardiograms using vector methods, 11 instances were encountered where the T waves at V_4 and V_5 were not consistent with the spatial concept of the electrical forces of the heart. In these 11 cases, the direction of the mean spatial T vector was such that the left anterior chest was an area of relative electrical positivity, and positive T waves should have been recorded from V_1 to V_6. Instead, at V_4 and V_5 negative T waves were recorded in these cases, while at all the other V-lead positions, positive T waves were recorded conforming with the direction of the mean spatial T vector.

As can be seen in figures 4 and 5 the contour of these negative T waves often closely resembles the "coved" ST-T pattern of recent myocardial infarction. Only when multiple precordial leads have been taken and are interpreted by vector methods can the two be confidently differentiated. Such differentiation is of considerable clinical importance because 5 of the 11 subjects were young adults with no clinical or historical evidence of organic heart disease, demonstrating that isolated T negativity may occur in the apparently normal subject. Others have described atypical precordial T-wave inversions which may be instances of isolated T negativity.[8–12] However, the relationship of this deformity to the electrical field of the heart as a whole and a rational method for its differentiation have not previously been presented.

In these 11 cases, the T-wave deformities were encountered only at electrode positions overlying the apical impulse, an extremely small region of the chest surface. In figure 4 are shown deflections recorded from all regions of the anterior chest and the T transitional pathway in 1 of these 11 subjects. The deflections were recorded at two inch intervals along a number of vertical lines on the anterior surface of the chest, and it can be seen that the area of isolated T-wave negativity occupies only a few square inches of chest surface with a narrow area of less marked T deformity surrounding it. Deflections from the remainder of the chest conform with the characteristics of the spatial T vector and the ST-T loop. This limited distribution of T deformity indicates that the responsible electrical force must be extremely small in magnitude. Furthermore, it indicates that the force must be generated from tissue immediately beneath the electrodes, for if it were generated from a deeper region it would be manifest over a larger area of chest surface. And finally, it will be noted that the force is only evident during the last third of the ST-T interval, having the appearance of a brief extrinsic electrical disturbance superimposed on an otherwise normal T wave. Not infrequently it appears as a V-shaped notch between what are usually identified as T and U waves; perhaps in figure 5*E* the deformity at V_4 and V_5 represents an instance of isolated T positivity.

How can one be certain this isolated T deformity is not simply due to the proximity of the electrodes to the myocardium at this region. That is, while at other regions of the chest the electrode is sufficiently remote from the myocardium so that all regions contribute relatively equivalently to the recorded deflections, here at the apex, potentials from the underlying portion of the myocardium dominate the recorded deflections, making them no longer consistent with the spatial concept of precordial lead deflections. There are two principal reasons why this is probably not the case. (1) Analogous deformity of the QRS complexes should have been observed at these same electrode positions, and was not. (To be sure, the frequency characteristics of potentials during the QRS period are different from those

during the T period, and this might have made a localized QRS deformity difficult to recognize. Technics have not been available to study this possibility.) (2) The mean spatial T vector is the resultant of T vectors from the various regions of the ventricular myocardium. In these cases, the direction of the mean spatial T vector was such that the T vectors for the individual regions of the myocardium were, in general, directed from endocardium to epicardium. Accordingly, if potentials from a given region of the heart should, because of proximity of the recording electrode, dominate the T forces as recorded at this region of the chest, an unusually high positive T wave should have been recorded, rather than the inverted T wave encountered in these cases.

This is of course not to deny that there are variations in the characteristics of T vectors generated from one region of the heart or another, nor that there are variations in the effective electrical remoteness of a given precordial electrode from various regions of the heart. Rather these cases indicate how rarely such differences have recognizable effects on body surface deflections when studied by present-day methods. It seems quite clear that, for clinical purposes in the vast majority of subjects, the resultant of all the T vectors, the mean spatial T vector, can with reasonable accuracy be considered to be the sole effective electrical force writing T waves in body surface leads wherever on the chest they may be taken.

Of course, it will always remain a possibility that an extremely small apical epicardial lesion will occur in a subject with a thin chest wall, and the electrical effects of this lesion will be too small in magnitude to recognizably alter the mean spatial T vector as registered in the remoter leads of conventional electrocardiography, but will influence the precordial deflection taken directly over it. However, from the present survey of several thousand consecutive tracings examined for this possibility, it is apparent that such instances must be extremely infrequent. In most subjects all regions of the body surface, including the region of the apex, are too remote from the heart to pick up these potentials selectively, with present methods for interpreting the deflections.

Because the electrical force causing the isolated T deformity is small in magnitude, superficial in origin, generated late in ventricular systole, and different from the majority of T forces in effective direction, it is possible that it is somehow related to the mechanical impact of the heart against the left anterior chest wall during systole. Suggestive evidence for this hypothesis was found in a subject with isolated T negativity who had auricular fibrillation with a markedly irregular ventricular rhythm (fig. 5*A*). In this subject, the contour of the T deformity at V_4 varied strikingly with the length of the preceding R-R interval, while T waves in remoter leads showed only slight variations in amplitude and no irregularity in contour in this regard. Thus, the magnitude of the electrical force causing the deformity varied with changes in the length of the preceding diastolic interval. Since the T wave is written during ventricular systole, the variations in the magnitude of the force must have been related in some way to variations in the systolic size of the heart as a consequence of the varying diastolic filling period. Such variations in systolic size would alter the intensity of the contact of the heart against the chest wall, accounting for the variations in the potentials generated at the region of contact.

Other studies were undertaken to elucidate the mechanism of isolated T-wave negativity. (1) It is well known that the application of cold to the myocardium markedly delays repolarization at the cooled region. It seemed conceivable that the outer layers of the myocardium at the apex might be "cooled" by their contact with the chest wall. However, application of heat and cold to this region of the precordium did not produce significant changes in the T deformity. (2) On full inspiration it was found that the T deformity dwindled or vanished. However, this finding did not greatly clarify the mechanism because it not only reduced the intensity of the mechanical contact of the heart against the chest wall, but also increased the distance between the heart and the electrode, thereby diminishing the recorded

amplitude of the force. The variation in isolated T negativity with the respiratory cycle is seen at V_4 in figure 5*B*. Chest compression was not found to produce isolated T negativity in normal subjects. (3) In 2 of the subjects with isolated T negativity but no other electrocardiographic abnormality 25 Gm. of potassium citrate were given orally. In normal subjects, this amount of potassium will produce a marked increase in the magnitude of the mean spatial T vector without altering its direction. In the subjects with isolated T negativity, the T waves on the precordium were increased in size but an isolated T deformity persisted.

There is, however, a serious shortcoming in this mechanical explanation for isolated T negativity. If it were due to the impact of the heart against the chest wall, one would expect the deformity to be encountered most commonly in subjects with cardiac enlargement and ventricular hypertension. However, this was not the case. Indeed, of these 11 cases, only 2 had arterial hypertension, 1 with cardiac enlargement, the other without. A third subject had cardiac enlargement due to arteriosclerotic heart disease without ventricular hypertension. The remaining subjects were free of recognizable organic heart disease, and 5 of these 8 subjects were males under 35 years of age.

In concluding this discussion of isolated T negativity, it is well to point out that an abnormal mean spatial T vector may occasionally have such a direction as to produce an apparent instance of isolated T negativity. Figure 5*C* illustrates this. Here, a 55 year old man with a clinical story and electrocardiographic evolution characteristic of recent myocardial infarction, the T vector has an abnormal direction and the transitional T pathway runs obliquely across the chest in such a way that V_4 lies in the area of relative negativity while all the other precordial leads lie in the area of relative positivity. The ST-T contours in the precordial V leads in this subject with myocardial infarction are nearly indistinguishable from those in figure 5*D*, an example of isolated T negativity obtained from a 27 year old male with no history or physical evidence of cardiovascular disease. The electrocardiogram in this latter case has been unchanged during six months follow-up.

Summary

1. A simple method for calculating spatial S-T and T vectors from conventional limb and precordial leads is presented, and the characteristics of these vectors in normal subjects are described.

2. It is suggested that the angle between the mean spatial QRS vector and the mean spatial T vector can be the basis for the clinical interpretation of electrocardiograms. This greatly simplifies interpretation and provides a rational and objective basis for the analysis of the electrocardiogram.

3. The commoner causes of abnormalities in the direction of the mean spatial S-T and T vectors are described.

4. A method for differentiating the normal from the abnormal electrocardiogram in the presence of digitalis effects is described.

5. An uncommon type of precordial T wave deformity is described: isolated T negativity. This deformity may be encountered in normal subjects and yet may present an ST-T contour indistinguishable from that of recent myocardial infarction. It is suggested that it may be related to the mechanical impact of the heart against the chest wall, and a method for differentiating it from other causes of T abnormality is presented.

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Catheterization of the Left Ventricle in Man

Study of Right Bundle Branch Block by Simultaneous Intracardiac Electrocardiography of Both Ventricles

By Morris F. Steinberg, M.D., Arthur Seligmann, M.D., Irving G. Kroop, M.D., and Arthur Grishman, M.D.

Simultaneous catheterization of the left and right ventricles was performed in a case of right bundle branch block. It was thought that in right bundle branch block the polarity of the initial deflection of the potentials obtained in the left ventricular cavity could be studied without interference of those contributed by the right ventricular cavity. A description of the technic employed is given. The results confirm those obtained in dogs. There is initial negativity of the potentials obtained within the left ventricular cavity.

CATHETERIZATION of the right cardiac chambers and pulmonary artery has been widely applied to the study of cardiac dynamics as well as to the analysis of cavity potentials. Since retrograde catheterization of the aorta had been successfully accomplished for direct aortography, it was felt that modification of such technics might permit catheterization of the left heart for the purpose of recording its cavity potentials. Such studies would be of particular interest in determining the spread of the excitation wave through the interventricular septum and might be accomplished best in subjects with right bundle branch block.

Method

The common carotid artery was exposed surgically under local anesthesia as for cerebral arteriography. A 13 gage needle was inserted through the vessel wall into which a purse string suture had been placed. With the needle directed toward the heart, a tightly fitting No. 5 French radiopaque metallic tipped catheter was slowly threaded into the artery. (A 16 gage needle fitted with a No. 3.5 French catheter was also found suitable.) The catheter was then positioned under fluoroscopic control. Passage through the aortic valve proved difficult and seemed to be accomplished best by allowing the catheter to form a coil, the blunt end of which entered the left ventricular cavity.

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Aided by grants from the Dazian Foundation for Medical Research, Percy and Harold Uris and Louis Adler.

The right cardiac chambers were catheterized in the usual manner by introducing a similar catheter into one of the antecubital veins. Spot roentgenograms were taken as permanent and accurate records of the location of both catheter tips whenever electrocardiograms were recorded. The Sanborn Tribeam Stethocardiette was employed throughout. All intracardiac tracings were taken at three times the conventional speed (75 mm. per second).

Material

A 76 year old white man was admitted to the hospital on Oct. 12, 1948 with the diagnosis of advanced metastatic carcinoma of the liver. The primary site was most probably in the gastrointestinal tract. The possible dangers of the procedure were explained and consent obtained. A routine electrocardiogram (fig. 1) showed right bundle branch block. The QRS complex was widened and measured 0.12 second. The RS-T segments were slightly depressed in leads V_2 to V_6. The T waves were low.

Catheterization of the left ventricle was performed from the left common carotid artery as described above. Simultaneously catheterization of the right ventricle was performed from the right antecubital vein. Following these procedures and the recording of the electrocardiograms illustrated, the patient developed a right hemiparesis and aphasia. These had improved by the time he was transferred to a chronic institution 10 days later.

Findings

1. With the tip of the left catheter situated above the aortic valve and the tip of the right catheter in the outflow tract of the right ventricle (figs. 2*A* and 3*A*), the following findings were noted: (a) *Left Side.* The peak of R of the atrial complex is reached at 0.06 second. The

ventricular complex shows a very small R wave with an initially slow then rapid downstroke. The deflections of higher amplitude are ended at 0.07 second and are followed by a low voltage biphasic deflection. The RS-T segment shows considerable positive displacement with upright T waves. Small U waves are also noted.

and the right catheter still in the right ventricular cavity as in 1 (figs. 2*B* and 3*B*), these findings were observed: *Left Side.* The ventricular complex has no R wave. The onset of the Q wave is synchronous with the Q wave of V_4. The initial phase is somewhat slower than the remainder of the complex. The S wave shows

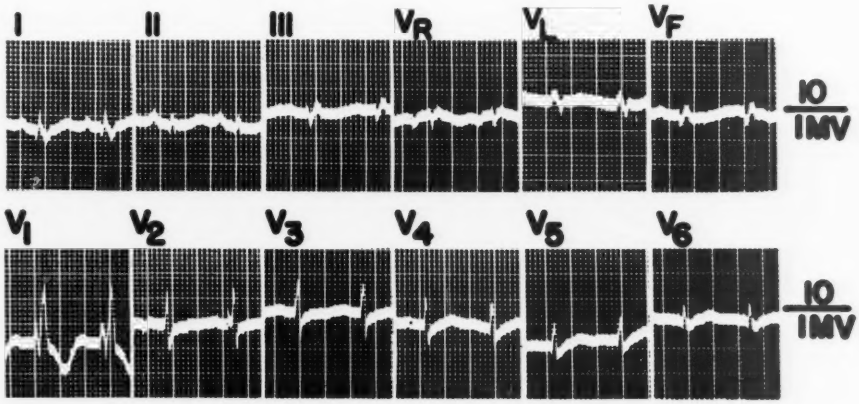

FIG. 1. Conventional electrocardiogram. Right bundle branch block is present.

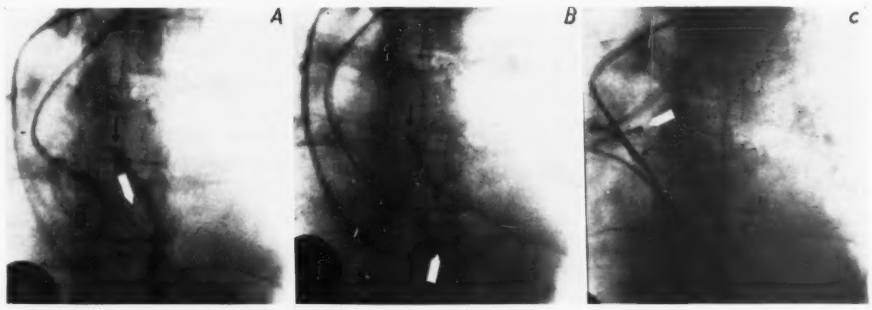

FIG. 2*A*. Left sided exploring electrode above aortic valve (white arrow). Tip of right sided electrode: outflow tract of right ventricle (black arrow). *B*. Tip of left sided electrode within the outflow tract of left ventricle (white arrow). Tip of right sided electrode as in 2*A*. *C*. Tip of left sided catheter in ascending aorta at approximate level of S-A node. Right sided catheter near the S-A node.

(b) *Right Side.* The ventricular complex consists of an initial high RS wave which reaches its peak 0.02 second after the beginning of the complex and is followed by an R′S′ at 0.085 second after the beginning of the complex. The RS-T segment shows a slight negative displacement followed by an inverted T wave.

2. With the tip of the left catheter situated within the outflow tract of the left ventricle

distinct notching which is synchronous with the upstroke of the R′ in V_1. A second QS-like complex of low amplitude follows the first and is almost synchronous with the R′S′ of the tracing simultaneously taken from the right ventricular cavity.

3. With the tip of the left catheter in the ascending aorta at approximately the level of the sinoatrial node and the right catheter

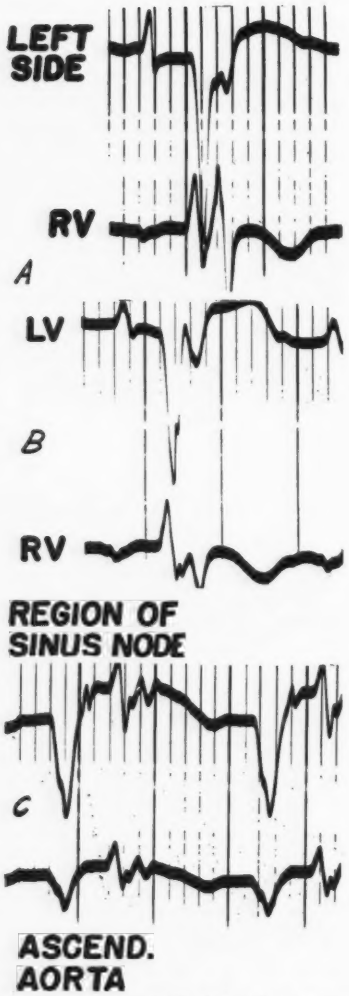

FIG. 3A. The catheter in the left side is above aortic valve (see fig. 2A). The ventricular complexes show a small R-wave. Right ventricular complexes show an RR′ pattern $\left(1\text{MV} = \frac{10}{10}\right)$.

B. Left ventricular cavity lead (see fig. 2B) shows an initially slow but entirely negative deflection. The configuration of the right ventricular complexes although somewhat different due to slight change of the electrode's position are basically similar to those shown in *A* $\left(1\text{MV} = \frac{10}{11}\right)$.

C. The catheter in the left ventricle is at the level of the S-A node. The catheter in the right ventricle is near S-A node. Note the striking similarity of atrial and ventricular complexes $\left(1\text{MV} = \frac{20}{11}\right)$.

near the sinoatrial node (figs. 2*C* and 3*C*), the following findings were noted:

Tracings from both ventricles show essentially the same features. The atrial complex consists of a deep QS wave, the total duration of which is somewhat more than 0.12 second. The ventricular complex reveals an RR′ pattern with a negative T wave, similar to the complex from the right ventricular cavity.

DISCUSSION

Wilson and his co-workers[1] produced right bundle branch block experimentally in dogs and recorded intracavity potentials. They reported the presence of an initial R followed by an S wave in the right ventricle while in the left ventricle complete negativity in the form of a QS wave was present. These findings have been corroborated by Sodi-Pollares and co-workers.[2] Hecht[3] studied 2 patients with right bundle branch block by catheterization of the right atrium but did not explore the right ventricle. Tracings taken at low atrial levels showed a small R and a deep S followed by a large R′ and small S′ in one case. In the other case, a similar pattern was found at upper atrial levels. The small R′ seen in the first case was absent but there was a short, deep Q followed by a notched R′. Sodi-Pollares and his co-workers[4] have reported their findings of the right intracavity potentials in human subjects with right bundle branch block and these corresponded to the findings in animal experiments: The ventricular complex consisted of an rsRS pattern followed by a negative T. The first small positive deflection (r) coincided with the initial R of V_1 while the late positive deflection (R) coincided with the ascending limb of R′ in V_1. These were interpreted as representing two separate phases of septal activation. The first represented the normal activation of the upper portion of the septum from the left to the right. The second represented abnormal activation of a lower portion of the septum below the point of block. These same authors also reported their findings in a patient with coarctation of the aorta and patent interatrial septal defect with congenital right bundle branch block. They were able to pass the catheter through the septal defect

and thus record left cavity potentials. The tracing showed a purely negative QS complex with a slurred initial deflection. The RS-T segment and T wave were positive.

Our study of the cavity potentials in a patient with right bundle branch block demonstrates that there is a completely negative initial deflection (QS) in the left ventricular cavity. The absence of positivity seems to support the contention that activation of the septum occurs initially on the left side. Our findings are in accord with those found in experimental right bundle branch block in dogs by Wilson and Sodi-Pollares and their co-workers,[1, 2] as well as those found in man by Sodi-Pollares.[4]

Because of the difficulties encountered in the technic of catheterization of the left ventricle, and because of the danger of cerebral complications, we feel that this procedure cannot be recommended. It is of interest to note that since our experience, Zimmerman, Scott and Becker[5] reported that they had catheterized the left ventricular cavity from the ulnar artery in 10 cases of aortic insufficiency. Their experience seems to confirm our opinion concerning the general hazards of this procedure. We feel that the left ventricular cavity may best be catheterized during lobectomy or pneumonectomy. Catheters could then be passed through a pulmonary vein into the left atrium and left ventricle.

Summary

1. The left ventricle in a human subject with an intact interventricular septum was catheterized via the common carotid artery.

2. Passage of the catheter beyond the aortic valve is difficult and may be impossible.

3. The occurrence of cerebral complications makes this procedure hazardous.

4. Simultaneously obtained intracavity potentials from both ventricles in human right bundle branch block are described.

5. The findings are in accord with those in canine experimental right bundle branch block. They are similar to the findings in another case of human right bundle branch block in whom the exploring catheter passed coincidentally from the right to the left side of the heart through an interatrial defect.

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Situs Inversus of the Abdominal Viscera with Levocardia

Report of Eight Cases Submitted to the Blalock-Taussig Operation

By MAURICE D. YOUNG, F.R.C.P. (CANADA), AND HERBERT E. GRISWOLD, M.D.

A search of the literature has revealed the reports of only 14 cases of situs inversus of the abdominal viscera with levocardia. Eight additional cases are presented in this paper. Angiocardiography and/or heart catheterization was carried out on 6 of these and a Blalock-Taussig operation was performed subsequently on each patient. The autopsy findings in 2 instances, together with the results of special investigations in surviving patients, indicate that the malformations are of a bizarre nature. Anomalies of the venous return to the heart are particularly common and variable degrees of transposition of the great vessels are postulated.

INVERSION of the abdominal viscera with levocardia is a rare anomaly in which the abdominal viscera are transposed but the heart occupies its normal position in the left chest. Forgacs[3] has recently reported two instances of this malformation and in a review of the literature found 12 previously reported cases; in every case there was a congenital anomaly of the heart. He implied that due to a paucity of reports no conclusion could be reached concerning the incidence of normal hearts associated with isolated transposition of the abdominal organs.

Inasmuch as only 14 cases have been reported in the literature, it seemed worthwhile to analyze 8 cases of situs inversus of the abdominal viscera with levocardia which have been studied in the cardiac clinic of the Harriet Lane Home. Taussig[5] has emphasized that the cardiac malformation is usually extremely complicated in such patients. Therefore, with two exceptions, special studies were carried out. In addition to the usual clinical examination and routine studies, angiocardiography* and/or cardiac catheterization† was performed on most of these patients. A Blalock-Taussig operation was carried out subsequently on each patient for the relief of inadequate pulmonary blood flow.

The cases are presented in abbreviated form with the autopsy findings in 2 cases and the postoperative progress of each of the remaining 6 patients. The blood analyses are summarized in table 1.

Case 1. C. F. HLH #A 48417: A 23 month old white female with moderate cyanosis and episodes of loss of consciousness. Examination revealed no cardiac enlargement. There was a soft systolic murmur but no palpable thrill. Fluoroscopy and x-ray films showed enlargement of the right ventricle, a concavity in the region of the pulmonary conus, a right aortic arch, and clear lung fields (fig. 1). Blood analysis revealed polycythemia and an extremely low oxgyen saturation of arterial blood of 7.5 per cent. (See table 1.)

The clinical diagnosis was tetralogy of Fallot with extreme pulmonary stenosis and a right aortic arch. A Blalock-Taussig operation was performed on the left side by Dr. Alfred Blalock on June 21, 1946, but the infant died during closure of the incision. At operation the superior vena cava was noted to lie on the left side.

Autopsy #20005. (Performed by Dr. J. H. Rid-

From the Department of Pediatrics, Johns Hopkins University, and the Cardiac Clinic, Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Md.

* The angiocardiograms were performed by Drs. Henry Bahnson and C. Rollins Hanlon of the Department of Surgery and Dr. Robert Cooley of the Department of Radiology, Johns Hopkins Hospital.

† All cardiac catheterizations and special physiologic tests were performed by Dr. Richard Bing and his associates of the Physiological Division of the Department of Surgery, Johns Hopkins Hospital.

ley). The pertinent findings involved the thoracic and abdominal viscera. On opening the abdomen a complete situs inversus of the abdominal viscera was found. There was a perfect mirror image of the usual relations: the stomach and spleen lay on the right side, the liver on the left, and the intestines were transposed. The left pleural cavity contained about 100 cc. of bloody fluid. The left lung was collapsed and was composed of two normally developed lobes and an additional rudimentary upper lobe. The right lung was made up of only two lobes but otherwise appeared normal to the naked eye. Microscopic sections showed patches of intrapulmonic hemorrhage, edema, and atelectasis. Only the alveoli of the right upper lobe were normally aerated.

FIG. 1. Case 1, C. F. Roentgenogram of chest showing concavity in the region of the pulmonary conus, right aortic arch, and clear lung fields.

The heart was predominantly on the left side. The aorta was seen to lie anteriorly to the pulmonary artery. The superior and inferior venae cavae entered the left or posterior auricle. The foramen ovale was patent and fenestrated. The pulmonary artery arose from the left or posterior ventricle, was atretic at its origin, and passed to the left lung only. The infundibulum and pulmonary valve were absent. The right or anterior auricle received the pulmonary veins. From this auricle the blood passed into a large thick-walled (9 mm.) right or anterior ventricle. The aorta was large and overrode the ventricular septum and arose primarily from this ventricle. The aorta ascended and descended to the right of the esophagus. Arising from the aorta through a wide orifice there was a short

TABLE 1.—*A Summary of the Blood Investigations Performed in Eight Patients with Situs Inversus of the Abdominal Viscera and Levocardia.*

Case No.	Time Interval	Blood Count			Arterial Blood Sample			
		R.B.C. (× 10^6 per cu.mm.)	Hgb. (Gm.)	Hct.	Oxygen Content (vols. %)	Oxygen Capacity (vols. %)	Oxygen Saturation	CO_2 Content (vols. %)
1. C. F.	Preoperative	7.4	20.5	70	1.9	25.3	7.5%	34.7
2. P. K.	Preoperative	8.95	23.2	74	19.5	35.25	55.5%	36.0
	3½ mos. Postop.	7.5	18.0					
	7 mos. Postop.	5.14	16.0					
3. C. H.	Preoperative	9.55	23.0	76	7.06	24.75	28.5%	38.5
	3 mos. Postop.	7.5	21.0	65				
	4 mos. Postop.	7.75	18.5	61				
4. T. B.	Preoperative	9.05	20.1	70	17.2	25.4	67.6%	37.6
	2 wks. Postop.	5.2	14.5	56			78.2%	
	2 yrs. Postop.	5.5	15.0					
5. R. C.	Preoperative	8.4	23.5	68	20.45	31.0	66.2%	38.9
	9 mos. Postop.	6.8	17.0	54	18.7	26.1	71.6%	
	21 mos. Postop.		15.8	48				
6. G. W. K.	Preoperative	8.45	22.5	71	20.5	31.7	64.8%	
	2 wks. Postop.	5.3	14.2	44				
	19 mos. Postop.		12.6					
7. J. E.	Preoperative	7.7	22.3	70	22.2	32.2	72%	42.0
	1 yr. Postop.	6.16	15.5	53	16.9	22.0	77%	
8. B. D.	Preoperative	9.9	24.2	82	19.9	34.0	58.5%	30.9
	2 mos. Postop.	5.9	17.0	52.5			88%*	
	1 yr. Postop.	4.27	13.5					

* By oximetry.

wide ductus arteriosus which bifurcated, sending one branch to the rudimentary pulmonary artery and the other branch directly to the right lung. The left subclavian artery arose from a left innominate artery. The surgical anastomosis of this vessel to the side of the left pulmonary artery was patent. One large bronchial artery passed to the right lung posteriorly.

Final Anatomic Diagnosis. Situs inversus of the abdominal viscera with levocardia. Atresia of the pulmonary orifice. Dilated aorta in dextroposition. Patent ductus arteriosus to the right lung with a small branch to atrophic pulmonary artery. Patent foramen ovale. Ventricular septal defect. Anomalous systemic and pulmonary venous return to the heart. Recent Blalock-Taussig operation. Atelectasis of the left lung.

FIG. 2. Case 2, P. K. Roentgenogram of chest showing cardiac outline with prominent pulmonary conus and right aortic arch.

Case 2. P. K. HLH #A 54017. A 10 year old white boy with moderate cyanosis and limited exercise tolerance. Examination revealed a harsh systolic murmur and a slight systolic thrill; there was no cardiac enlargement. X-ray films and fluoroscopy revealed slight prominence in the region of the pulmonary conus and slightly increased lung markings but no pulsations were visible in the lung fields (fig. 2). There was a right aortic arch. The stomach was seen to lie on the right side and the liver lay on the left side. Blood analysis revealed a marked polycythemia; the oxygen saturation of an arterial blood sample was 55.5 per cent. (See table 1.) The electrocardiogram showed right axis deviation and hypertrophy of the anterior ventricle.

The angiocardiograms were interpreted as showing an overriding aorta and a high ventricular septal defect; the pulmonary artery was poorly visualized. The standard exercise test[1] showed a drop in the oxygen consumption. The pulmonary capillary blood flow determined by the indirect test[1] was low.

This boy was considered to have situs inversus of the abdominal viscera with levocardia, a pulmonic stenosis with a ventricular septal defect and an overriding aorta. A Blalock-Taussig operation was performed successfully by Dr. Alfred Blalock on April 8, 1947. Following operation the patient gradually developed cardiac failure, from which he died seven months later.*

Autopsy #3894-47. (Performed by Dr. A. H. Wells and Dr. H. H. Jaffe.) The chief interest centered about the heart and abdominal organs. The heart was in its normal position, with the apex toward the left. There was obvious hypertrophy of the right side. The heart was enlarged and weighed 230 Gm. (normal 110 to 135 Gm.). There was complete absence of the auricular septum and absence of the upper third of the ventricular septum. The common auricular cavity was grossly enlarged to about three times the combined size of two normal auricles, and the cavity of the right ventricle was about three times its normal size. The cavity of the left ventricle was quite small and admitted the tips of two fingers.

The aorta arose from the right or anterior ventricle and did not override the ventricular septal defect. It lay anteriorly and to the right of the pulmonary artery which arose from the left or posterior ventricle. The pulmonary valves were fused so that there was only a slitlike opening measuring 8 mm. in length. The pulmonary artery was very small beyond the valve and did not measure more than 1 cm. in diameter at any point in its course.

The aorta measured approximately 2 cm. in diameter in its ascending portion. The proximal end of the innominate artery was anastomosed to the side of the left pulmonary artery. The anastomosis was patent and the intimal surface of the vessels was quite smooth and apparently covered by endothelium. The ductus arteriosus was obliterated.

A large vein, believed to be a left superior vena cava, crossed from left to right anteriorly to the aortic arch and received the pulmonary veins from both lungs. This vein entered the right superior vena cava which passed into the right side of the single auricle. The inferior vena cava was in its normal position. The origin of an anomalous vein thought at operation to be the inferior vena cava was not determined.

There were 300 cc. of clear fluid in the right pleural cavity. The right lung was well aerated and slightly emphysematous. The left lung was covered by dense fibrous adhesions and was almost completely atelectatic. There was moderate congestion throughout

* For the interval history and for the report of the autopsy findings we are indebted to Dr. Roy C. Pederson, Dr. A. H. Wells, and Dr. H. H. Jaffe of Duluth, Minn.

both lungs, but no consolidation. Both lungs had three lobes.

Each of the abdominal viscera lay in a transposed position so that there was a perfect mirror image of the normal relations. The liver extended 6 cm. below the left costal margin; it weighed 1450 Gm. (normal 700 to 800 Gm.) and showed severe chronic passive congestion.

The anatomical diagnosis was: Cor triloculare biventriculare. Situs inversus of the abdominal viscera. Transposition of the great vessels. Pulmonary stenosis. Hypertrophy of the right ventricle. Huge ventricular septal defect. Anomalous pulmonary venous return to the heart. Chronic congestive heart failure. Complete atelectasis of the left lung.

Comment. These 2 cases illustrate the complicated anatomy which may be present in a patient who has situs inversus of the abdominal viscera and levocardia. In each patient there was a mirror image of the normal relations of the abdominal viscera and a complicated malformation of the heart. Certain features were similar; namely, the inadequate pulmonary blood flow with considerable enlargement of the right ventricle, the anomalous pulmonary venous return to the right side of the heart, the transposition of the great vessels, and the ventricular septal defect.

In other respects the malformations were different. In case 1, the foramen ovale was patent and the systemic veins entered the left auricle. The aorta arose primarily from the right ventricle but overrode the ventricular septum. There was pulmonary atresia so that the pulmonary circulation was maintained through a patent ductus arteriosus, a rudimentary pulmonary artery, and the bronchial arteries. Theoretically, the patient should have benefited from an increase in the blood supply to the lungs, but she died suddenly at the conclusion of the operation. The cause of death was not apparent, but it would seem that the production of an artificial ductus arteriosus placed too sudden a strain on the heart. In case 2, there was a complete absence of the auricular septum and the systemic veins entered the single auricle in their normal position. The right superior vena cava received blood from the pulmonary veins by way of the left superior vena cava. The aorta arose entirely from the right ventricle and did not override the ventricular septum; the ductus arteriosus was obliterated. The left ventricle was small and underdeveloped. There was marked pulmonic stenosis, but apparently there had been sufficient blood flow through the pulmonary vessels to maintain life. Immediately following operation this patient developed cardiac failure from which he died seven months later. In this instance, therefore, death was not immediate, but the altered circulation led to slowly progressive heart failure.

These patients are the only 2 in this series on whom autopsies have been performed and concerning whom the exact nature of the malformations is known. However, in each of the remaining patients, with but one exception, investigations demonstrated the existence of a complicated cardiac malformation.

Case 3. C. H. HLH #A 60487: A 15 month old white female with moderate to marked cyanosis, a harsh croupy cough, and attacks of paroxysmal dyspnea. There was no cardiac enlargement; no thrill was palpable and no murmurs were audible. The liver edge was palpable under the left costal margin. Fluoroscopy showed that the heart was boot-shaped in outline and there was a left aortic arch; the lung fields appeared abnormally clear; a pulmonary artery was visible on the right side only; the stomach and liver were transposed. Electrocardiography displayed right axis deviation and hypertrophy of the anterior ventricle. There was marked polycythemia and a low arterial blood oxygen saturation of 28.5 per cent. (See table 1.)

Angiocardiography demonstrated a left superior vena cava and a small pulmonary artery on each side, and the films were interpreted as showing an auricular septal defect, pulmonic stenosis and an overriding aorta. (See fig. 3.) The preoperative diagnosis was situs inversus of the abdominal viscera with levocardia, tetralogy of Fallot with an auricular septal defect, a left aortic arch and a left superior vena cava.

An anastomosis was performed between the end of the right subclavian artery and the side of the right pulmonary artery by Dr. Alfred Blalock on May 4, 1948. As expected, no superior vena cava was found on this side. The immediate postoperative progress was uneventful and there was temporary improvement in the patient's condition. Subsequently she developed generalized edema, cardiac enlargement and evidence of renal failure. She died six months after operation from cardiac failure and anuria with uremia and convulsions. Permission for autopsy was not granted.

Comment. This patient is the third in this series who died following a Blalock-Taussig

operation. Cardiac failure with progressive cardiac enlargement was gradual in onset, but as in case 2 the patient died approximately six months after operation. In this instance the the right both in the angiocardiogram and at operation. It may be postulated, therefore, that there may have been a transposition of the great vessels as in case 2.

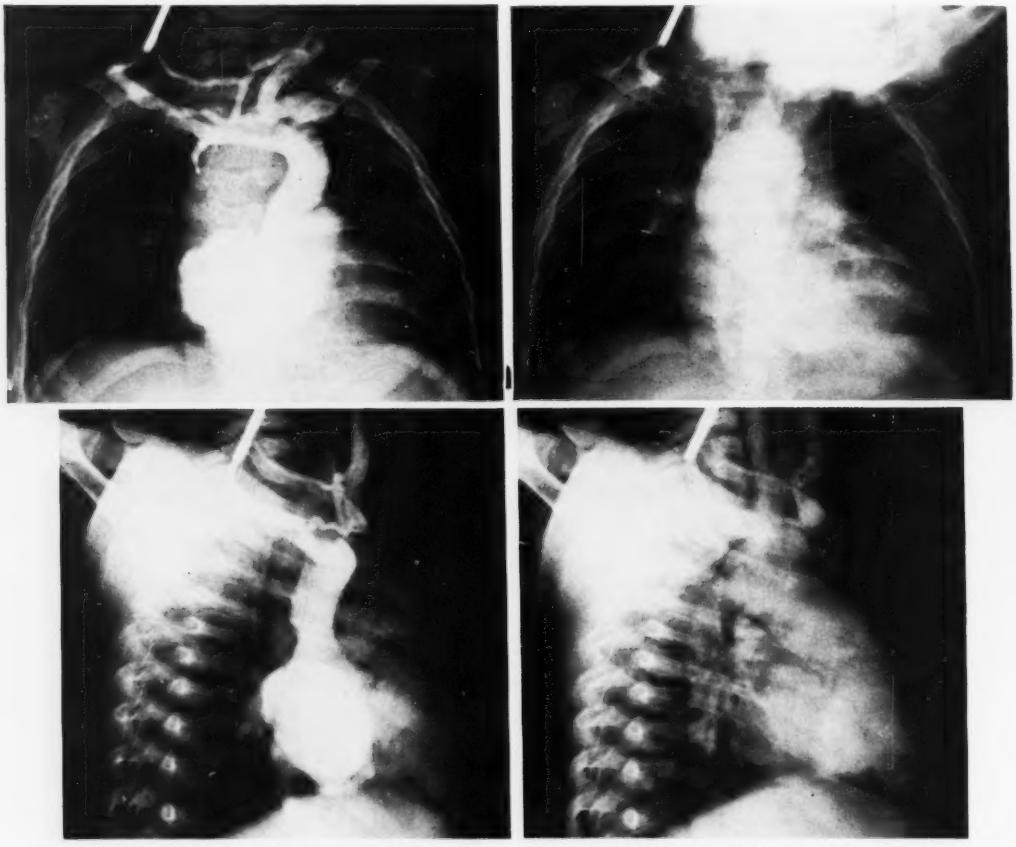

FIG. 3. Case 3, C. H. Angiocardiogram. Injection through right external jugular vein. *Top left:* Anteroposterior view (1 to 2 seconds) showing left superior vena cava and early filling of both auricles. *Top right:* Anteroposterior view (2 to 3 seconds) showing early visualization of aorta which appears to arise more to the right than normal, sweep upwards to the right before crossing to form a left aortic arch, and descend on the left. *Bottom left:* Oblique view (1 to 2 seconds) showing filling of both auricles. *Bottom right:* Oblique view (2 to 3 seconds) showing early visualization of aorta which appears to arise anteriorly.

urinary findings suggested that death was due to a combination of cardiac failure and renal insufficiency. The exact nature of the cardiac malformation is not known. Clinical and radiologic evidence pointed to the existence of an anomalous systemic venous return, an auricular septal defect, and pulmonic stenosis. The aorta was seen to arise anteriorly and far to

Case 4. T. B. HLH #A-53589. A 4 year old white boy with marked cyanosis and brief periods of unconsciousness. On examination a systolic thrill was palpable and a harsh systolic murmur was audible over the precordium. Fluoroscopy revealed that the heart was not enlarged; there was a slight concavity in the region of the pulmonary conus; the lung fields appeared clear; the aortic arch was on the right side; the stomach was on the right, and the liver shadow was on the left side. The electro-

cardiogram showed right axis deviation and a predominance of the anterior ventricle. Blood analyses revealed marked polycythemia, and an arterial blood oxygen saturation of 67.6 per cent. (See table 1.)

Angiocardiography, performed on two occasions on the right and left sides respectively, revealed bilateral superior venae cavae, one to each auricle, a normal origin of the pulmonary artery, a ventricular septal defect, and an overriding aorta. Cardiac catheterization, also carried out on each side, confirmed the presence of two superior venae cavae.

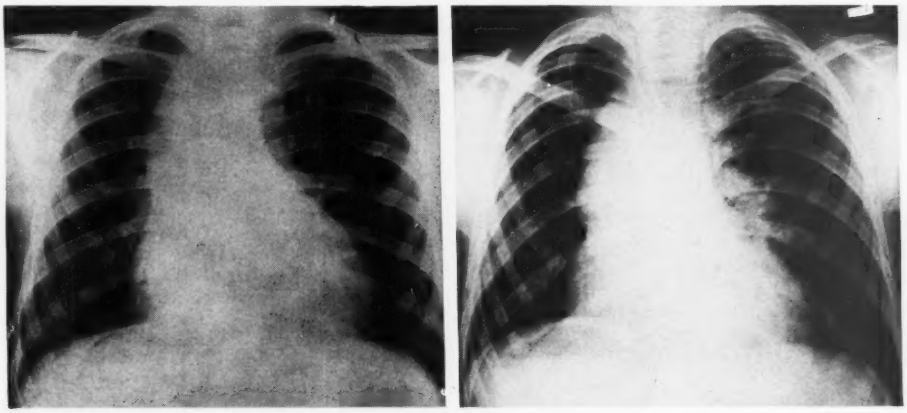

FIG. 4. Case 5, R. C. Roentgenograms of chest. *Left:* Preoperative film showing cardiac enlargement with a broad basal shadow and right aortic arch. *Right:* Postoperative film showing increase in lung markings with little change in heart size.

The results obtained from this investigation were as follows:

	Pressure (*mm. Hg.*)	Blood O_2 Content (*vols. %*)
R. sup. vena cava		15.4
R. auricle		15.3
R. ventricle	80/12	15.1
L. sup. vena cava		10.3
L. auricle	25/11	20.4
L. ventricle	129/8	19.9

Femoral Artery—content 19.9 vols. %
—capacity 26.5 vols. %
—saturation 75%

On the assumption that the blood returning from the lungs was 96% saturated, the oxygen content of the blood in the pulmonary veins was calculated to be 25.6 vols. per cent.

The results were interpreted as indicative of inadequate pulmonary blood flow and an anomalous return of at least one pulmonary vein to the right superior vena cava.

The preoperative diagnosis was situs inversus of the abdominal viscera with levocardia, pulmonary stenosis, overriding aorta with a right aortic arch and anomalous return of the pulmonary and systemic circulations. A Blalock-Taussig operation was performed by Dr. Alfred Blalock on April 1, 1947; the postoperative progress was uneventful. The patient was reported to be remarkably improved 22 months after operation.* He was able to walk an almost unlimited distance and had only residual cyanosis. At that time a humming continuous murmur was audible over the base of the heart. His heart had enlarged but there was no evidence of cardiac failure. The results of blood examination are included in table 1.

Case 5. R. C. HLH #A 54377: An 8½ year old white boy with limited exercise tolerance in whom heart disease was diagnosed at the age of 1 year, but in whom cyanosis did not appear until between the ages of 3 and 4 years. The heart was enlarged to the left; a systolic thrill was palpable and both a systolic murmur and a faint diastolic murmur were audible. The liver was palpable under the left costal margin. Fluoroscopy revealed a generalized cardiac enlargement with a broad shadow at the base; the lung markings were slightly prominent but no pulsations were visible; the aortic arch was on the right side; the stomach was on the right, and the liver was situated on the left. X-ray films of the chest confirmed these observations (fig. 4). The electrocardiogram revealed left axis deviation and predominance of the posterior ventricle. There was polycythemia; the arterial blood oxygen saturation was 66.2 per cent (see table 1).

Angiocardiography revealed a left superior vena cava and prompt filling of the aorta. On cardiac

* For this report, dated March 16, 1949, and for permission to refer to it, we are indebted to Dr. M. Cooperstock of Marquette, Michigan.

catheterization the catheter passed down a left superior vena cava and appeared to enter the right auricle through the coronary sinus and thence passed to the left auricle; it was impossible to pass the catheter into a ventricle. The oxygen content of the superior vena cava blood was 18.1 vols. per cent, of the right auricle blood 20.5 vols. per cent, and of the left auricle blood 29.4 vols. per cent. The oxygen content of the blood in the pulmonary vein (obtained by catheterization) was 29.4 vols. per cent. The total pulmonary capillary blood flow was calculated to be 1730 cc. per minute per square meter of body surface.* These findings indicated the presence of a left superior vena cava, an auricular septal defect, and a low pulmonary blood flow.

In view of the pulmonic stenosis and the right to left intracardiac shunt, a Blalock-Taussig anastomosis was performed by Dr. Alfred Blalock on April 25, 1947. At operation a large vein, considered to be the inferior vena cava, was found to enter the left superior vena cava.

This boy's postoperative progress was uneventful.† His exercise tolerance has increased greatly. Examination nine months after operation revealed only mild cyanosis without clubbing of the fingers; a loud continuous murmur was audible; the heart was almost identically the same size as before operation and there was no evidence of cardiac failure. The results of postoperative blood examinations are shown in table 1.

Case 6. G. W. K. HLH #A 57195: A 9½ year old white boy with marked cyanosis and limited exercise tolerance. At the age of 8 years he had contracted a severe throat infection complicated by a septicemia, heart failure and auricular fibrillation. Upon examination the heart was normal in size; a systolic thrill was palpable and a widely transmitted harsh systolic murmur was heard. The liver was felt on the left side and the stomach resonance was on the right. Fluoroscopy revealed clear lung fields; the heart was not enlarged in the anterior-posterior view but in the left anterior oblique position there appeared to be enlargement of the anterior ventricle; there was a left aortic arch. Blood count revealed a polycythemia; the arterial blood oxygen saturation was 64.8 per cent. (See table 1.) The electrocardiogram showed a tendency to right axis deviation and hypertrophy of the anterior ventricle.

Angiocardiography demonstrated a left superior vena cava; the pulmonary artery appeared to arise posteriorly to the aorta.

A standard exercise test showed a fall in the oxygen consumption from 31 to 22 cc. per liter ventilation. Cardiac catheterization revealed a high right ventricular pressure of 100/3 mm. Hg. Analysis of the blood samples revealed the following:

	Blood O_2 Content *vols. %*
R. sup. vena cava	20.5
R. auricle	25.4
R. ventricle	22.1
Pulmonary vein (catheterized via right auricle)	29.6
Femoral artery—content 20.5 vols. %	
—capacity 31.7 vols. %	
—saturation 64.8%	

The lower oxygen content of the blood in the femoral artery compared to that in the right ventricle may be explained by the fact that, as suggested by the angiocardiogram, a left superior vena cava probably entered the left heart, thereby reducing the oxygen content of blood in the left ventricle and hence in the femoral artery. These findings indicated an anomalous pulmonary venous return to the right auricle and/or an auricular septal defect. Determination of the pulmonary blood-flow was impossible owing to the probability of an abnormal origin of the pulmonary artery.

The diagnosis of the nature of the malformation was not difficult. There were two superior venae cavae. The posterior position of the pulmonary artery relative to the aorta, combined with the anomalous pulmonary venous return and the drainage of one superior vena cava into the left auricle, suggested the possibility of a corrected transposition of the great vessels. The occurrence of persistent cyanosis indicated that the anomaly was of an even more complicated nature. Inasmuch as there was clinical, fluoroscopic and physiologic evidence of pulmonary stenosis and a right to left intracardiac shunt, a Blalock-Taussig operation was recommended. The anastomosis was made between the proximal end of the right subclavian artery and the side of the right pulmonary artery by Dr. C. Rollins Hanlon on Sept. 12, 1947. The immediate postoperative progress was smooth. Following operation a continuous murmur indicative of blood flow through the anastomosis was readily audible. A follow-up report‡ 19 months after operation stated that he was able to walk 2 miles and indulge in mild sports; he was not visibly cyanotic at rest. A continuous murmur was audible over the right upper chest. Blood examination revealed a hemoglobin reading of 12.6 Gm.

Case 7. J. E. HLH #A 59569: A 6½ year old white girl with persistent cyanosis, limited exercise tolerance, and dyspnea. Examination revealed a

† According to the formula of Bing and associates.[1]

* For this report and for permission to refer to it we are indebted to Dr. Marvin Schwartz of Portland, Oregon, and for the arterial blood analysis we wish to thank Dr. Elton Watkins of the University of Oregon Medical School.

‡ For this report, dated April 29, 1949, and for permission to refer to it, we are indebted to Dr. N. B. Livingston, Jr., of Mohall, North Dakota.

systolic thrill and a high-pitched widely transmitted systolic murmur; the heart was not enlarged; the liver was palpable under the left costal margin. Fluoroscopy revealed a concavity in the region of the pulmonary conus but the pulmonary arteries and the pulmonary vascular markings were more prominent than expected. There was a right aortic arch. The stomach was seen on the right side. The electrocardiogram revealed right axis deviation and preponderance of the anterior ventricle. Blood examination showed a polycythemia; the arterial blood oxygen saturation was 72 per cent. (See table 1.)

The angiocardiogram was interpreted as demonstrating a left superior vena cava, small pulmonary arteries and a large aorta which appeared to arise far anteriorly; the appearances were considered to be consistent with the diagnosis of tetralogy of Fallot.

The following results were obtained from cardiac catheterization:

	Pressure *mm. Hg.*	Blood O_2 Content *vols. %*
R. sup. vena cava		17.8
R. auricle		19.6
R. ventricle	92/2	20.8
Pulmonary artery	8/0	19.9
Pulmonary vein (catheterized)		29.6
Femoral artery—content 21.2 vols. %		
—capacity 30 vols. %		
—saturation 71%		

From these figures the pulmonary artery blood flow was calculated to be 1620 cc. per minute per square meter of body surface, and the systemic blood flow was calculated to be 4100 cc. per minute per square meter of body surface[1]; thus there was a right to left shunt of 2480 cc. On the basis of the low pulmonary artery flow and the low pulmonary artery pressure associated with the high right ventricular pressure, it was felt that there was pulmonic stenosis. The difference between the oxygen content of the blood in the superior vena cava and that in the right auricle suggested that there was either an aberrant return of one or more of the pulmonary veins to the right auricle and/or an auricular septal defect.

In view of the inadequate pulmonary blood flow and the evidence of a right to left intracardiac shunt, a Blalock-Taussig operation was performed by Dr. W. P. Longmire on April 6, 1948. Following operation the patient developed a high fever, and blood cultures yielded organisms identified as either alpha or gamma streptococci. After intensive penicillin therapy the bloodstream infection eventually was cured. The patient was discharged home 2 months after operation.

Since discharge from the hospital her progress has been very satisfactory. She tires less easily and is less dyspneic. She is able to walk a mile with ease and has been riding a tricycle. Examination 11 months after operation revealed minimal clubbing of the fingers and barely perceptible cyanosis at rest. A well-marked blowing continuous murmur was audible over the left upper chest anteriorly and posteriorly. Her heart had increased in size but there was no evidence of cardiac failure. Blood count at that time revealed a mild polycythemia; the oxygen saturation of an arterial blood sample was 77 per cent.

Case 8. B. D. HLH #A 61973: A 5 year old boy with marked cyanosis and considerable limitation of activity. An attempt to perform a Blalock-Taussig anastomosis in France had been unsuccessful. Upon examination he was poorly nourished and poorly developed. The heart was slightly enlarged. No thrill was palpable and only a faint systolic murmur was audible. The liver was palpable in the epigastrium. Fluoroscopy revealed a slightly enlarged heart, boot-shaped in outline; there was a concavity in the region of the pulmonary conus and the lung fields appeared quiet. There was a right aortic arch. The stomach was seen on the right side and the liver lay on the left. The electrocardiogram showed right axis deviation and anterior ventricular hypertrophy. The blood count revealed marked polycythemia; the oxygen saturation of an arterial blood sample was 58.5 per cent (see table 1).

The clinical diagnosis was situs inversus of the abdominal viscera with levocardia and tetralogy of Fallot. In April 1948 Dr. Alfred Blalock made an anastomosis between the end of the left subclavian artery and the side of the left pulmonary artery. The patient's postoperative progress was relatively uneventful. Digitalis therapy was instituted because of tachycardia and some enlargement of the liver.

Following operation the patient showed distinct improvement. Examination two months later revealed an easily palpable systolic thrill, a loud blowing systolic murmur, and in addition a well-marked blowing continuous murmur. The polycythemia was less and there was a considerable rise in the arterial blood oxygen saturation. (See table 1.) A follow-up report* a year after operation stated that he was then able to walk 1½ miles without fatigue. No cyanosis was visible at rest, he was not dyspneic, and he had gained weight. A continuous murmur was easily heard. There had been a further drop in the blood count.

Discussion

An analysis of the cases presented in this series supports the impression that cardiac mal-

* For this report, dated April 11, 1949, and for permission to refer to it, we are indebted to Prof. Donzelot, Dr. Cottraux, and Dr. A. Pithon of the Broussais Hospital, Paris.

TABLE 2.—*Summary of Findings.*

Case No.	Sex	Age	Clinical Diagnosis	Aort. Arch	ECG	Exercise Test	Heart Catheterization	Angiocardiography	Preoperative Diagnosis	Operative Findings	Operative Pathology	Operation	Remarks
1. C. F.	F.	23 mo.	Tetralogy of Fallot	R	—	—	—	—	Tetralogy of Fallot	Small P.A. Minimal pulsation	Left S.V.C. L. innom. A. P.A. branched very early	L. subcl. to L. pulmonary anastomosis	Died during skin closure. *Autopsy:* S.V.C. & I.V.C. to L. aur. Patent foramen ovale. P.A. atretic at origin & transposed. Overriding aorta mainly from R. vent. Ventricular septal defect. Absent pulm. infundib. & pulm. valve. Pulm. veins returned to R. auricle. Pulm. circ. via P.D.A. & bronchial A.
2. P. K.	M.	10 yr.	Tetralogy of Fallot	R	RAD RVH	Drop—25 to 19	Indirect test—low pulmonary flow.	Overriding aorta. High ventricular sept. def. P.A. poorly seen.	Pulmonary stenosis. Vent. sept. defect. Overriding aorta	Small P.A. Weak pulsation	L. sup. pulm. vein to large anomalous vein to left S.V.C. to R. side. L. innomin. A.	L. innominate to L. pulm. anastomosis.	Died 7 months after operation. *Autopsy:* Single auricle. Transposition of great vessels. Venae cavae to R. side of auricle. Pulm. veins to left S.V.C. to right S.V.C. Huge ventricular septal defect. Marked pulmonary stenosis. 3 lobes in each lung.
3. C. H.	F.	15 mo.	Tetralogy of Fallot	L	RAD RVH	—	—	Left S.V.C. Auricular septal defect. Dextroposed aorta (?transp.) Small P.A.	Tetralogy of Fallot. Aur. sep. def. Left S.V.C.	Fairly large P.A.—weak pulsation.	Aorta far to right No S.V.C. on right.	R. subcl. to R. pulmonary anastomosis.	Died 6 months after operation. No autopsy. Progressive cardiac failure. ? Nephritis. Transposition of great vessels postulated.
4. T. B.	M.	4½ yr.	Tetralogy of Fallot	R	RAD RVH	—	Pulm. vein to right superior vena cava. Low pulm. blood flow. Bilateral S.V.C.	Bilat. S.V.C. Ventricular septal defect. Overriding aorta. Small P.A.	Pulmonary stenosis. Overriding aorta. Anom. syst. & pulm. ven. return.	Fairly large P.A.—low pressure.	Left S.V.C. Oblit. ductus to L. subcl. A. L. innomin. A.	L. subcl. to L. pulmonary anastomosis.	*2 yrs. Postop.:* Progress very satisfactory. Tolerance almost unlimited. Residual cyanosis; humming murmur. C/T ratio 54.9% on 8.9.48. (preop. C/T ratio 48.3%). No arterial oxygen studies.
5. R. C.	M.	8¼ yr.	Pulmonary stenosis. ? Tricusp. atresia	R	LAD LVH	Drop—29 to 19	Left S.V.C. to R. auricle. Low pulmonary blood flow. Auricular septal defect.	Left S.V.C. Overriding aorta. Films unsatisfactory.	Pulmonary stenosis. Overriding aorta.	Large P.A. No pulsation.	Large anomal. vein (? I.V.C.) to left S.V.C. L. innomin. A.	L. subcl. to L. pulmonary anastomosis.	*2 yrs. Postop.:* Progress satisfactory. Plays games, rides bicycle. Gain of 19 lbs. in weight. Mild cyanosis at rest. Loud continuous murmur. C/T ratio 58.8% on 1.25.49. (pre-op. C/T ratio 69%). Arterial O_2 71.6% in January 1948. (preop. arterial O_2 66%)

6. G. K.	M.	9½ yr.	Tetralogy of Fallot	L	RAD RVH	Drop—31 to 22	Right S.V.C. to R. aur. Low pulmonary bloodflow. Auric. septal defect or pulm. vein to R. auricle.	Left S.V.C. to L. auricle. Aorta anterior to P.A. ? Transposition of great vessels. ? Single ventricle.	Tetralogy of Fallot. Anom. pulm. ven. return or corrected transposition Aur. sep. def. Pulm. stenosis. Bilat. S.V.C.	Large P.A. Low pressure	—	R. subcl. to R. pulmonary anastomosis.	*19 mos. Postop.:* Progress satisfactory. No cyanosis at rest. Can walk 2 miles. Plays games. Gain of 21 lbs. in weight. Increase of 4 ins. in height. Good continuous murmur.
7. J. E.	F.	6½ yr.	Tetralogy of Fallot	R	RAD RVH	—	Right S.V.C. Low pulmonary bloodflow. Pulm. vein to R. auricle or aur. septal defect.	Left S.V.C. possibly entering L. auricle. Aorta arose far anteriorly & overriding, ? transposed. Small P.A.	Tetralogy of Fallot. Anom. pulm. ven. retur or auricular sep. defect. Bilat. S.V.C.	Low P.A. pressure	L. innomin. A.	L. subcl. to L. pulmonary anastomosis	Developed septicemia after operation. *1 yr. Postop.:* Progress satisfactory. Walks 1 mile with ease. Less fatigue and less dyspnea. Gained 6 lbs. in weight. Cyanosis barely perceptible. Good continuous murmur. C/T ratio 57.9% on 3.10.49. (preop. C/T ratio 51.3%) Arterial O_2 77% (preop. 72%).
8. B. D.	M.	5 yr.	Tetralogy of Fallot	R	RAD RVH	—	—	—	Tetralogy of Fallot	Large P.A. Low pressure	L. innomin. A. Obliterated ductus to L. subcl. A. No S.V.C. noted on left.	L. subcl. to L. pulmonary anastomosis.	*10 mo. Postop.:* Progress satisfactory. Walks 1½ miles without fatigue. Gained 6 lbs. in weight. No dyspnea and no cyanosis. Clubbing scarcely noticeable. Normal life, no squatting. Intense continuous murmur. No arterial oxygen studies.

Abbreviations: S.V.C.—Superior vena cava
I.V.C.—Inferior vena cava
P.D.A.—Patent ductus arteriosus
P.A.—Pulmonary artery
RAD—Right axis deviation
RVH—Right ventricular hypertrophy.

formations are complicated when they exist in combination with situs inversus of the abdominal viscera and levocardia. The findings in the individual patients are summarized in table 2.

The presence of situs inversus of the abdominal viscera may be easily overlooked, particularly in the patient who is severely incapacitated and whose tolerance is low since under such circumstance examination has to be rapid. Such an oversight occurred in case 1. Unless the liver is palpable, clinical examination offers no clue to the existence of situs inversus. In order to ensure correct diagnosis it is therefore advisable to make a practice of lowering the fluoroscope screen after each esophagram in order to locate the position of the stomach. When a patient with a congenital cardiac defect is found to have situs inversus of the abdominal viscera, a complicated malformation should be suspected and further investigations should be carried out in an attempt to elucidate more accurately the nature of the malformation.

The mortality from operation in this group is high. Three of the 8 patients died. This is distinctly higher than the mortality with the Blalock-Taussig operation performed by the same group of surgeons in cases of simple tetralogy of Fallot,[6] but is to be expected from the bizarre nature of the malformation. Although statistics in such a small group are apt to be erroneous, the serious risk of operation deserves mention. In another respect the group resembles the cases of simple tetralogy of Fallot in that the deaths occurred at the time of operation or within about six months thereafter; those who survived the first six months have continued to progress satisfactorily.

Evidence is abundant that there was inadequate pulmonary blood flow in every patient in this series. Clinical examination and fluoroscopy indicated that this was so; heart catheterization demonstrated it in cases 4, 5, 6, and 7; angiocardiography revealed small pulmonary arteries in cases 2, 3, 4, and 7; and in every instance at operation the pulmonary artery pressure was considered to be low. In the 2 cases which came to autopsy complete atresia of the pulmonary artery was found in case 1 so that the pulmonary circulation was maintained through a patent ductus arteriosus and a large bronchial artery, and in case 2 there was a marked pulmonary stenosis.

It is noteworthy that the aorta arched to the right in 6 of the 8 patients. As is usual in a person with a right aortic arch, in each of these 6 cases the innominate artery was situated on the left, i.e. the aorta and its main branches lay in the mirror image of the normal relations. In each of 2 instances (cases 4 and 8) an obliterated ductus arteriosus was seen at operation to extend from the left subclavian artery to the pulmonary artery.

Analysis of the 7 cases in which data in addition to the clinical findings are available reveals certain striking features. Anomalies of the systemic venous return to the heart were found in all 7 cases. Bilateral superior venae cavae were found in 4 patients (cases 2, 4, 6, and 7). In case 4 the right and left superior venae cavae were known to have entered respectively the right and left auricles, while the same was considered probable in both case 6 and case 7. In case 2 the left superior vena cava crossed to enter the right superior vena cava and both emptied into the right auricle. In cases 1, 3, and 5, a single superior vena cava was demonstrated on the left side in each instance. The venae cavae entered the left auricle in case 1, the superior vena cava emptied into the right auricle through the coronary sinus in case 5, and in case 3 the site of termination of the superior vena cava could not be ascertained.

Anomalies of the pulmonary venous return were demonstrated in 3 instances (cases 1, 2, and 4) and were suspected in 2 others (cases 6 and 7). In both cases 1 and 2, all pulmonary veins were found at autopsy to enter the right side of the heart. In case 4, at least one pulmonary vein was demonstrated by heart catheterization to enter the right superior vena cava; in case 6 one or more of the pulmonary veins appeared to drain into the right auricle since the catheter apparently entered a pulmonary vein directly from the right auricle. However, the possibility that the catheter slipped through an auricular septal defect into the left auricle and thence into a pulmonary vein cannot be entirely excluded. It was suspected on heart

catheterization that one or more of the pulmonary veins entered the right auricle directly in case 7, but this could not be proved as an auricular septal defect may produce similar findings. An auricular septal defect was known to exist in each of 2 patients as it was demonstrated by angiocardiography in case 3 and by heart catheterization in case 5; in case 1 there was a patent foramen ovale and in case 2 a single auricle was found at autopsy. Thus of the 7 cases under discussion, a communication between the auricles was known to exist in 4 patients, was suspected in one (case 7) and could not be excluded in a sixth (case 6).

Prior to operation in every instance the aorta was believed to override the ventricular septum. However, at autopsy the aorta was found to be transposed in case 2 and to arise mainly from the right ventricle in case 1. The possibility that the position of the aorta was a factor in the failure of the heart to withstand the strain of the altered circulation after operation has to be considered in each of these cases. A similar possibility has to be borne in mind in case 3, as the aorta was seen in the angiocardiogram to be dextroposed and a diagnosis of transposition of the aorta was considered. In case 6 the angiocardiogram demonstrated that the aorta lay anteriorly to the pulmonary artery and in case 7 the aorta was seen to arise far anteriorly. In each of these last 2 instances transposition of the aorta is therefore a possibility, but both these patients have progressed well since operation in contrast to the first 3 patients, so that there must be additional factors involved.

The pulmonary artery arose from the left ventricle in case 1 and also in case 2. In these cases, therefore, there was a complete transposition of the great vessels, although in case 1 the aorta did override the septum to a mild degree. Since the pulmonary venous return was to the right auricle and the systemic venous return was to the left auricle in case 1, the malformation amounted to a corrected transposition of the great vessels with an overriding aorta. In case 2 the pulmonary veins entered the superior vena cava so that blood from both the systemic and the pulmonary circulations entered the right side of the single auricle. In this instance, therefore, there was a partially corrected transposition of the great vessels inasmuch as the aorta, pulmonary artery and pulmonary veins were transposed. A similar but not identical malformation may have been present in both case 6 and case 7. In the former, the origin of the pulmonary artery was seen in the angiocardiogram to lie posteriorly to the aorta, and it was known after heart catheterization that one or more of the pulmonary veins probably entered the right auricle; furthermore, there was a left superior vena cava which appeared to empty into the left auricle. These findings led to the consideration that a corrected transposition of the great vessels may have been present. That this was not the complete picture was demonstrated by the fact that there was also a right superior vena cava which entered the right auricle. Almost identical possibilities were present in case 7, except that the exact relation of the aorta to the origin of the pulmonary artery was not clearly visualized in the angiocardiogram although the aorta was seen to arise far anteriorly.

In case 3, there is less evidence to support consideration of the possibility of a transposition of the great vessels. Nevertheless, the aorta was seen to arise far to the right both on angiocardiography and at operation. In addition the superior vena cava was seen in the angiocardiogram to be on the left side and at operation no superior vena cava was found on the right side. Therefore, there is at least a suggestion of the possibility that a corrected transposition of the great vessels was combined with some other anomaly.

Thus, in brief, a corrected transposition of the great vessels combined with pulmonary stenosis existed in case 1, and a partially corrected transposition of the great vessels was present in case 2 and may be postulated in each of cases 3, 6, and 7.

The pathogenesis of the cardiac defects in cases of isolated inversion of the abdominal viscera has been discussed by Forgacs.[3] Of the 14 cases in his review, the auricles were transposed in 8, there was a common auricle in each of 2, and in 4 cases the disposition of the auricles could not be ascertained. In his article he attempted to correlate the findings in this group

with those in cases of isolated dextrocardia, and pointed out that transposition of the auricles may be regarded as the fundamental defect in most cases of each group. According to his argument, the transposition of the auricles is dependent upon the embryonic abdominal venous channels. A reversal of the normal relation between heart and liver is associated with a corresponding change in the hepatic venous channels, with the result that in cases of situs inversus of the abdominal viscera the venous drainage is to the left instead of to the right side of the heart. This theory was also advanced by Lochte.[4]

On the whole, our series supports this view. However, it is apparent that in some cases the transposition is incomplete. In consequence various degrees of transposition of the venous return to the heart are to be expected in combination with various degrees of transposition of the great vessels. Some of the variations are exemplified by the cases in this series.

Summary

1. Eight cases of congenital malformations of the heart of the cyanotic group occurring in association with situs inversus of the abdominal viscera with levocardia have been presented in abbreviated form.

2. The bizarre nature of the malformations has been demonstrated by heart catheterization, angiocardiography, operative findings, and in 2 cases at autopsy.

3. A summary of the findings in each case is given in table 2.

4. Analysis of the cases has been undertaken wherever available data have permitted. This analysis reveals that (a) Situs inversus of the abdominal viscera may be easily overlooked. (b) The mortality from operation in this group is relatively high. (c) Inadequate pulmonary blood flow was demonstrated in every case in our series. (d) The aorta and its main branches bore a mirror image relationship to the normal anatomy in 6 of the 8 cases. (e) Anomalies of the systemic venous return to the heart are very common in this type of malformation, and in this series occurred in 7 of the 8 cases. (f) Anomalies of the pulmonary venous return were demonstrated in 4 cases and suspected in one additional case. (g) A communication between the auricles was found in each of 4 cases and was suspected in 2 additional cases. (h) The aorta was dextroposed in each case; it was completely transposed in one case, and mainly transposed in another; the possibility of transposition of the aorta is postulated in 3 further cases. (i) Transposition of both great vessels was demonstrated in 2 cases and postulated in 3 other cases.

5. The likelihood of a corrected transposition of the great vessels in each of 5 of the 8 cases is discussed.

6. The possible pathogenesis of the cardiac defects is briefly mentioned.

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Cortisone Therapy in Acute Rheumatic Carditis: Preliminary Observations

By T. N. Harris, M.D., W. B. Abrams, M.D., T. F. P. Leo, M.D., and J. P. Hubbard, M.D.

Four patients with acute rheumatic carditis of moderate to severe degree were treated with cortisone. After a latent period of 5 to 15 days, there was fairly rapid subsidence in temperature, erythrocyte sedimentation rate and some other signs of inflammation. After cessation of the course of cortisone therapy, there was evidence of recrudescence of rheumatic activity in all four patients. In three of these the therapy was resumed, with quite unusually rapid decline in the fever and sedimentation rate. The cardiologic signs showed no improvement throughout the entire period of observation.

FOLLOWING the dramatic results reported for cortisone therapy in rheumatoid arthritis by Hench, Kendall and coworkers,[1] these authors applied this hormone to the treatment of 3 patients with acute rheumatic fever and reported a rapid subsidence of fever, tachycardia, polyarthritis, elevated sedimentation rates, and abnormal electrocardiographic changes.[2] A later report by the group, which included studies on 8 additional patients (4 given cortisone and 4 given adrenocorticotropic hormone, confirmed the earlier findings.[3] In addition, however, it was noticed that 2 of the patients treated with cortisone suffered recurrences of rheumatic activity when the administration of cortisone was discontinued. Resumption of the use of cortisone abolished the evidence of activity in both cases. Massell[4] has reported favorable results in the treatment of a series of 14 cases of acute rheumatic fever with ACTH.

The obvious importance of these findings led us to institute the experimental treatment with cortisone of patients with acute rheumatic carditis who were under close clinical observation. It was decided to choose for the first phase of the study a group of patients whose degree of cardiac involvement was more severe than seemed to be the case in the patients studied by Hench and his associates. Although thus far only 4 patients have been included in this study, certain observations which were made seemed to warrant the reporting of these preliminary data.

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This study was supported by grants from the Life Insurance Medical Research Fund, The Helen Hay Whitney Foundation and the United States Public Health Service.

Methods and Materials

The 4 patients included in this study all had definite carditis of moderate or severe degree. They were hospitalized in the two institutions from which this study is reported. They ranged in age from 4 to 22 years.

The patients were examined physically at least every two days by two or three of the authors. Laboratory examinations included the erythrocyte sedimentation rate (ESR), white blood cell count, and hemoglobin concentration. Electrocardiograms were taken as required. The sedimentation rate was determined by a method described elsewhere.[5] It involved a series of readings of the erythrocyte level at five minute intervals, in order to determine the rate of free fall of the corpuscles, and a correction for the relative volume of erythrocytes.

Blood counts of eosinophilic polymorphonuclear leukocytes were done by the Thorn technic.[6] Antistreptolysin and streptococcal antihyaluronidase titrations of serum were done as described elsewhere.[7, 8]

The dosage of cortisone employed was 112.5 mg. for the 3 older patients, whose weights were, in every case, approximately 90 pounds, and 75 mg. for the 4 year old patient. These doses were somewhat higher than those used by Hench. They were maintained at a level

which caused substantial decrease in the blood eosinophil count, but did not give rise to glycosuria or to concentrations of blood sugar over 120 mg. per 100 cc. in the fasting state.

Results

1. *Effect on Fever.* In 3 of the patients the temperatures promptly fell following the first administration of cortisone, reaching normal in 4 to 7 days. In the fourth, J. K., the temperature fell gradually, reaching a plateau in 17 days.

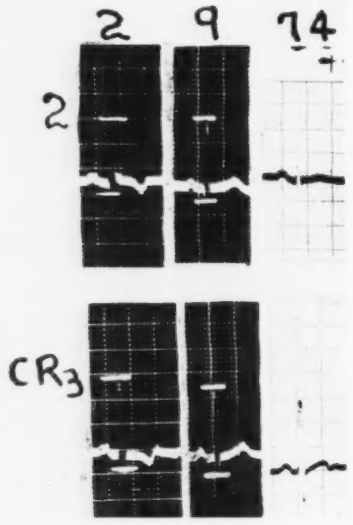

Fig. 1. Case 1, M. B. Day 2. Lead II: elevated S-T segments, inverted T waves. CR_3: inverted T waves. Day 9. Lead II: very slightly elevated S-T segments, upright T waves. CR_3: upright T waves. Day 74. Lead II: low T waves. CR_3: inverted T waves.

When cortisone was readministered to 3 patients the temperatures, which had risen on cessation of cortisone therapy, fell even more sharply, reaching normal in 1, 3, and 6 days respectively.

2. *Effect on Polyarthritis.* When cortisone was first administered to the 2 patients complaining of joint pains, both were free of pain within 4 days.

Three patients complained of joint pains on cessation of cortisone therapy. These patients were free of pain again within 4 days after resumption of the hormone.

3. *Effect on Sedimentation Rate.* In three cases the sedimentation rates fell to within the limits of normal in 9, 16 and 21 days, respectively, after the beginning of cortisone therapy. The sedimentation rate of the fourth patient (F. M. W.) reached a plateau after 28 days of such treatment.

When cortisone was reinstituted to combat exacerbations, the sedimentation rates fell to within normal limits in 7, 10 and 17 days.

4. *Effect on the Clinical Cardiac Status.* In 3 patients heart failure developed 4, 10 and 20 days after the institution of cortisone, as indicated by hepatic enlargement, pleural effusion, ascites and edema. This condition responded well to the usual therapeutic measures while the hormone therapy was continued. All murmurs present at the beginning of the period of observation were present at the end. In addition, 3 of the patients acquired a new murmur while under treatment. M. B. developed a blowing, early diastolic apical murmur in addition to the apical systolic blow she first presented. F. M. W. developed a decrescendo early diastolic murmur and a crescendo presystolic murmur at the apex during her first course on cortisone and these have persisted. Furthermore, the decrescendo diastolic murmur heard only at the second left intercostal space when she was first observed could be heard transmitted past the cardiac apex during the latter part of this period. In addition to the aortic and double apical murmurs initially present in J. K., an aortic systolic murmur appeared.

Roentgenographic studies in 3 patients over the period of this study have shown no change in cardiac size or contour of the heart. All were initially enlarged: slightly in B. D.; markedly in M. B.; and extremely in J. K. The early cardiac x-ray films of F. M. W. were normal. Later, however, definite left ventricular enlargement with some fullness of the pulmonary artery segment was demonstrable.

5. *Effect on the Electrocardiograms.* (*a*) M. B.: The electrocardiogram taken two days before cortisone was instituted (fig. 1, day 2) showed right axis deviation; slight elevation of the QRS-T segments in leads II, III, and aV_F, and

inversion of the T waves in leads II, III, aV_F, and all precordial leads. Eight days later, six days after cortisone was started, the T waves were upright in all leads except III and CR_2. The QRS-T elevations were very slight (fig. 1, day 9). The T waves continued to improve and the tracing was within normal limits during the second course of cortisone. Twenty days later, six days after cortisone was finally discontinued, some minor changes in the T waves of the precordial leads were noted. Ten days later all T waves had decreased in amplitude and were again inverted in CR_{2-4} (fig. 1, day

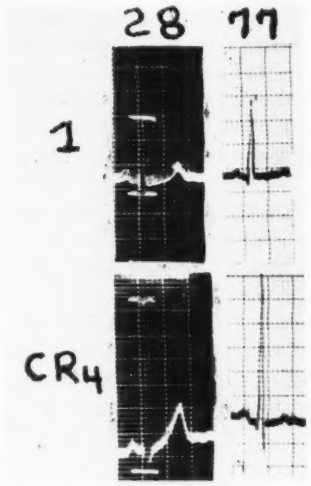

FIG. 2. Case 3, F. M. W. Day 28. Normal ECG. Day 77. Prolonged Q-T intervals. Lead I: flattened T waves. CR_4: diphasic T waves.

74). A week later the T waves in the chest leads showed a definite tendency to become more inverted.

(*b*) B. D.: The initial electrocardiogram showed only notched P waves and a sinus tachycardia. Ten days later, after nine days of cortisone treatment, increased amplitudes of the QRS complexes and the T waves were noted. An electrocardiogram taken 22 days after cortisone was discontinued showed top-normal Q-T intervals, left axis deviation, low amplitudes of the QRS complexes, and persistently notched P waves.

(*c*) F. M. W.: The electrocardiographic tracings taken before and during her first course of cortisone were normal (fig. 2, day 28). A tracing taken six days before cortisone was

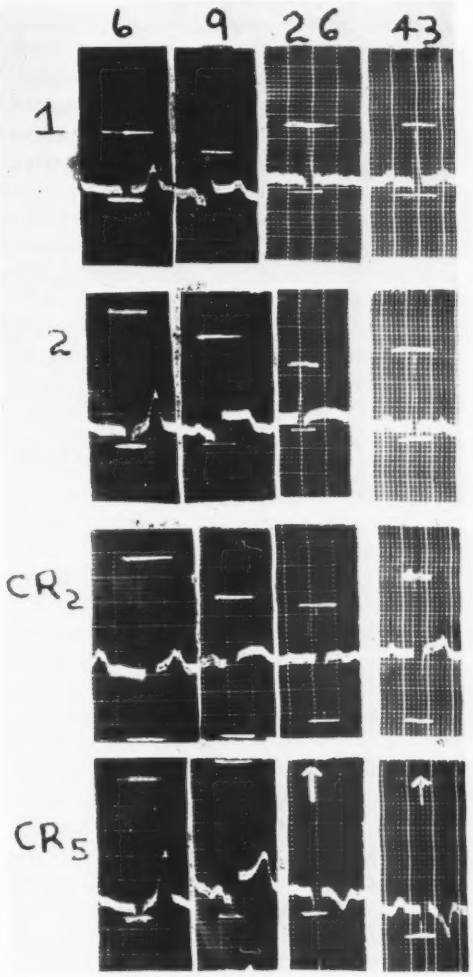

FIG. 3. Case 4, J. K. Day 6. Prolonged P-R intervals (the P waves are best seen superimposed on the T waves in lead CR_2. Day 9. Elevated S-T segments, normal P-R intervals. Day 26. Auricular fibrillation. Leads I and CR_2: flattened T waves. Lead CR_5: inverted T waves. Day 43. Prolonged P-R intervals. Leads I and CR_2: improvement of T waves. Lead CR_5: deepening of T waves. Horizontal lines have been drawn in to demonstrate the height of the R waves and the depths of the Q or S waves.

stopped for the second time was normal, but the voltage of the T waves was lower.

Ten days after cortisone treatment was

stopped her electrocardiogram showed a prolonged Q-T interval and flattened or diphasic T waves in nearly all leads (fig. 2, day 77). Five and ten days later, repeated tracings were the same.

(*d*) J. K.: The initial electrocardiogram showed a markedly prolonged P-R interval (fig. 3, day 6). Daily tracings showed a rapid shortening of the P-R interval until it became normal three days after cortisone was first given. At the same time, however, the QRS-T segments became progressively more elevated as pericarditis developed (fig. 3, day 9). They reached a peak and began to descend four days after the drug was started, reaching the base line 16 days later. Auricular fibrillation was recorded on tracings taken 8, 20 and 21 days after the institution of therapy. On the tenth day of treatment the T waves began to be inverted in leads I, aV_L, and CR_{4-6}, and this trend has progressed and persisted. On the twenty-first day the T waves of CR_{3-5} also became inverted (fig. 3, day 26).

An electrocardiogram taken at the height of the exacerbation that followed the first cessation of cortisone therapy showed the reappearance of prolonged P-R intervals and notched P waves. The T waves were better but still deeply inverted in the left precordial leads (fig. 3, day 43).

A tracing taken three weeks later showed a shorter P-R interval and some improvement in the T waves. An electrocardiogram made one month later showed a normal P-R interval but the T waves were still flat. The patient was receiving digitalis after Jan. 8, 1950.

6. *Serologic Observations.* Sera were prepared from each blood specimen drawn from these patients and examined for their content of antistreptolysin and streptococcal antihyaluronidase. The titers of these antibodies decreased during the period of observation, but whether the rate of this decrease is significantly greater in patients with rheumatic fever under cortisone treatment than in control patients can be decided only after a considerably larger number of patients has been studied.

Summary of Clinical Data

The sequence of events during these courses of treatment, then, followed this general pattern: For the first 5 to 15 days after the beginning of treatment with cortisone there was either no objective improvement or there was actual clinical evidence indicative of exacerbation or spread of the inflammatory process. Thereafter, there was fairly rapid subsidence of the signs of inflammation, *per se*, so that the temperature, pulse rate and erythrocyte sedimentation rates were within the normal range or, in one case, at a slightly elevated plateau, within three weeks of treatment, without a corresponding improvement in cardiac findings, other than some electrocardiographic changes. At this time, when the general signs of inflammation had subsided, and the cardiac signs had ceased to show change, cortisone was withdrawn. Within two to nine days after this there was in each case an exacerbation, with the same clinical picture as had characterized the beginning of that episode in that patient. In 3 of the 4 patients cortisone therapy was reinstituted, and within three to seven days all of these 3 showed a rapid improvement in the general signs of inflammation. The cardiac signs, however, showed little or no change during the few days following withdrawal or reinstitution of cortisone therapy. Following the rapid improvement in general signs at the beginning of the second course of treatment, it was possible to reduce the dosage of the drug until the drug was withdrawn completely within two weeks. In 2 patients elevation of the temperature and sedimentation rate followed this withdrawal. These were probably due to terminal activity of the rheumatic inflammation, and were followed by unfavorable electrocardiographic changes within 6 to 10 days.

Discussion

These data are not presented as a basis for clinical evaluation of cortisone in the treatment of rheumatic carditis. Such evaluation would require the study of a far greater number of patients over a longer period of time, and the inclusion of such special groups as those patients with acute rheumatic carditis in whom the diagnosis can be made and treatment instituted within the first few days of the episode. However, these limited observations are being presented because they may suggest certain

generalizations or problems regarding the mechanisms involved.

First, the sequence of clinical events on cessation and resumption of cortisone therapy would seem to indicate strongly that one or more of the physiologic functions or pharmacodynamic effects of the hormone must be closely related to some mechanism involved in the pathogenesis of rheumatic inflammation. Thus it is probable, regardless of the ultimate role of cortisone therapy in rheumatic carditis, that the results of laboratory investigations of cortisone may have significant applications to the problem of the mechanisms involved in rheumatic infection.

Second, it is of interest to compare the effects of cortisone in these patients on the signs of infection of the body as a whole and on the evidences of inflammation of cardiac tissue. Although the response of these patients to cortisone was quite satisfactory in terms of the period of elevation of temperature, pulse rate and erythrocyte sedimentation rate during the first course of treatment, and quite dramatic during the second course, the cardiac signs did not correspondingly show changes which could be said to compare favorably with those seen in patients with acute rheumatic carditis treated symptomatically, since 3 of the 4 patients had auscultatory signs of more extensive cardiac involvement at the conclusion of the total course of cortisone therapy than at its inception, and only 1 patient had cardiac signs which were definitely as good at the end of the treatment. The fact that in this particular sampling of patients some showed changes of this sort, in spite of the generally favorable course of all 4 patients, suggests the possibility of a curious dichotomy between the effects of cortisone on the cardiac changes and those on the signs of inflammation of the body as a whole. These data also suggest the possibility of a difference between the clinical results in rheumatic carditis and those which the drug has been shown to have in rheumatoid arthritis. In the cases of the latter condition treated with cortisone, as described by Hench and his co-workers and by others, functional and even histologic improvement of the inflamed organ, the joints, accompanied the return of the sedimentation rate to normal limits and the general clinical improvement. In the 4 patients with acute rheumatic carditis treated with cortisone in the present study, not only did the chief seat of inflammation, the heart, fail to improve functionally as the general signs of inflammation subsided, but, as is mentioned above, in 3 out of the 4, there were clinical evidences of extension of the pathologic process. Thus, it would appear that no matter what the final evaluation of cortisone as a therapeutic agent in rheumatic carditis, there may be a difference between the effects of this drug in rheumatoid arthritis and those in rheumatic fever.

Summary

Four patients with acute rheumatic carditis of fairly severe degree were treated with cortisone. After three weeks, when the temperature, erythrocyte sedimentation rate and pulse rate had returned to approximately normal limits and cardiac signs had ceased to show change, the cortisone therapy was terminated. Within a few days thereafter each of the patients showed a sharp exacerbation of signs of rheumatic infection, and on resumption of cortisone therapy these signs disappeared quite rapidly. The general signs of inflammation thus seemed to respond fairly well to this treatment.

However, the cardiac signs were worse in 2 of the patients and questionably so in a third patient of the group at the conclusion of the course of treatment in comparison with the findings before cortisone therapy was instituted.

Case Reports

1. M. B., a 22 year old Negro woman, was admitted to the hospital on Dec. 26, 1949 in her first known attack of rheumatic fever, complaining of dyspnea, ankle edema, sore throat, and pain in the left knee of six days' duration. Her temperature was 102 F. orally and her pulse rate 90. She was dyspneic and orthopneic, and complained of severe chest pain. A low-pitched blowing systolic murmur was heard at the apex and a to-and-fro friction rub was heard at the base of the heart. Rales were audible over the bases of the lungs. The liver edge was felt 6 cm. below the right costal margin. Studies on admission showed the following: Chest x-ray films showed: pericardial effusion and small bilateral pleural effusion; the ECG showed inverted T waves in leads II and III, aV_F and all precordial leads, and slight S-T elevation in II, III and aV_F. Laboratory studies: (for brevity, the corrected erythrocyte sedi-

mentation rate, in mm. per hour, will be indicated by ESR; white blood cell count per cu. mm. by WBC; hemoglobin concentration, in grams per 100 cc. of blood, by Hb; electrocardiogram by ECG: dates will be conventionally abbreviated.) ESR: 87; Hb: 8.1; WBC: 12,500.

Cortisone therapy was instituted on 12/29/49, nine days after the onset of the illness. She had been receiving aspirin from the time of admission to 12/28/49. The patient continued to become worse. On 1/1/50 the respiratory rate was 60, and the dyspnea was so distressing as to require the administration of oxygen. She was severely ill for the next two days, and then began to show a number of signs of improvement.

In the ECG of 1/3/50 all the abnormally inverted T waves had become upright. Her temperature fell to normal by 1/4/50 and the ESR fell from over 110 on 12/30/49 to 18 on 1/13/50. The friction rub was no longer audible on 1/9, at which time the dyspnea was considerably decreased, and an x-ray film on 1/13 showed cardiac enlargement but no pericardial effusion. The liver could not be palpated or percussed on 1/19. Cortisone was discontinued on 1/19, at which time her disease process was subsiding but not inactive. Her apical systolic murmur had become more harsh and blowing in character, and was now transmitted to the midaxillary line. A diastolic third heart sound was occasionally heard at the apex. The Hb had risen to 10.1 Gm., and the WBC had fallen to 10,700.

Her convalescence continued uneventfully until 1/23, when she complained of precordial pain. Dyspnea reappeared and the pulse rose from 100 to 130. On 1/24, her temperature was 101 F. Bilateral pleural effusion reappeared and increased until 1/27 when it began to resolve. She complained of pain in the shoulders on 1/26 and pain in the right knee on 1/27. Oxygen therapy was necessary from 1/24 to 1/27. The ESR rose from 23 on 1/23 to 90 on 1/25 and 110 on 1/28. Her liver edge descended to 5 cm. below the right costal margin. The ECG showed only a sinus tachycardia.

Cortisone was restored on 1/25 at a dosage of 112.5 mg. per day, and was later briefly raised to 150 mg. per day. Her temperature immediately began to fall, reaching normal in three days. Other symptoms and signs which were on the upgrade when cortisone was restored continued to become worse for three more days and then fell off rapidly. The ESR fell from 110 on 1/28 to 20 on 2/1, and her dyspnea had disappeared by this day. She had no joint or precordial pains after 1/27. The ECG of 1/30 was within normal limits. The pulse rate fell from 120 on 1/20 to 84 on 1/30. The dosage of cortisone was gradually reduced. The drug was discontinued on 2/15, at which time the dosage was 3 mg. per day.

Three days after the cortisone was stopped, she complained of coryza. The ESR rose to 30, then, four days later, to 75. Her temperature rose to 100 F. orally. Without further treatment she again became afebrile in three days and her ESR became normal within a few days. The Hb rose to 10.8

At this writing the patient feels well. The signs of inflammation are gone, but there is cardiac enlargement, mitral insufficiency with transmission of the murmur to the posterior axillary line, and an occasional early diastolic apical blowing murmur. Inversion of the T waves in her ECG has recurred. Some of the clinical features of this case history are presented in figure 1.

In view of the greater sensitivity of the elevated ESR than leukocytosis as evidence of activity of the rheumatic process,[9] and of the recent observation of leukocytosis in children under treatment with ACTH, by Hain and Wilson,[10] it is very probable that the leukocytosis noted in the case history and chart is indicative of effective levels of cortisone and not of activity of the rheumatic infection.

2. B. D., a 4 year old Negro girl, was admitted to the hospital on Jan. 12, 1950 complaining of severe epistaxis, fever, malaise and anorexia of one day's duration. On admission the child was acutely ill, with a rectal temperature of 104 F. and a cardiac rate of 160. A blowing systolic murmur (which had been present before this episode) was heard, with maximal intensity at the apex and transmission to the midaxillary line. Initial laboratory studies showed the following: ESR: 85; WBC: 16,500; Hb: 8.0; ECG: sinus tachycardia; chest x-ray films: globular heart with prominence of the upper right border and suggestive mitralization of the left border; cardiothoracic ratio: 0.62.

A diagnosis of acute rheumatic fever was made and cortisone therapy was instituted three days after the onset of the illness at a dosage of 75 mg. per day. Her temperature began to descend on the second day of treatment and was normal by the fourth. Similarly her pulse rate fell to 100 to 110. The ESR, which was 100 on the first day of treatment, fell to 60 on the sixth day and to 15 on the tenth day.

The patient, however, did not reflect the favorable appearance of her clinical chart. She remained listless and anorexic. When her heart rate became slower, a blowing early-diastolic apical murmur became audible. On 1/23, 10 days after cortisone was started, she suddenly developed edema of the face and legs, ascites, hepatomegaly, further cardiac enlargement (her apex beat moved down and to the left), and a sleeping pulse rate of 148. Serum sodium and potassium concentrations were within normal limits. An x-ray film of the chest showed evidence of early congestive changes. To combat the acute decompensation, oxygen therapy, Theocalcin, and a salt free diet were employed. Penicillin and aureomycin were administered because of the fear of a complicating pneumonia. On this regimen her edema melted away, so that by 1/31 she had returned to a state

similar to that prior to the acute heart failure. All the special measures except Theocalcin were discontinued. The ESR at this time was 12. The next few days were characterized by notable subjective improvement. On 2/1 the dose of cortisone was reduced to 22.5 mg. per day, and on 2/2 it was stopped.

On 2/4 it was noticed she was lethargic and had slight but definite ankle edema. When questioned she complained of a sore throat. Her temperature was 104 F., rectally, and her pulse rate 168. The ESR rose from 6 on 2/4 to 22 on 2/8. Penicillin was administered. The patient improved gradually until 2/7 when she suffered three severe nosebleeds. Her temperature, which had been falling gradually, reached normal on 2/9, five days after its sudden rise. Her pulse rate fell to a range of 100 to 140. Penicillin was stopped on 2/9. Her course since has been one of steady subjective improvement.

Studies during this period showed the following: the Hb rose from 7.0 to 9.4; the WBC fell from 18,600 to 5,850; two ECG tracings were within normal limits. However, a tracing taken on 2/23 showed a top-normal Q-T interval, QRS complexes of low amplitude, and left axis deviation.

At this writing her illness has been apparently quiescent for three weeks and her convalescence is continuing. Physical examination shows the apical systolic and diastolic murmurs have persisted. A chest x-ray film made on 2/23 shows the heart to be the same size and shape as at the onset of her illness.

3. F. M. W., a 13 year old Negro girl, was admitted to the hospital on December 15, 1949 in her first known episode of rheumatic fever, complaining of fever, sore throat, pain and redness of one knee, nosebleeds, and abdominal pain of four days' duration.

In the hospital the fever and abdominal pain were soon overshadowed by excruciating pain, swelling, and tenderness of the elbows, knees and ankles. Physical examination showed, in addition to the arthritis, a blowing, decrescendo, diastolic murmur confined to the second intercostal space to the left of the sternum, and a soft, blowing, systolic, apical murmur transmitted only to the anterior axillary line. Other studies during this initial period yielded these average values: WBC: 18,150; Hb: 9.2; and ESR: 105.

A diagnosis of acute rheumatic fever was made and cortisone was started on 12/29 at a daily dose of 150 mg., which was reduced to 112.5 mg. after two days. On the day cortisone was started she presented the following findings: temperature: 104 F.; ESR: 105; WBC: 17,300; and Hb: 7.2.

The temperature immediately began to fall, reaching normal after three days of treatment. The joint pains were slightly eased for two days, then rapidly improved until 1/2/50, when, after four days of cortisone, she was free of pain. Her ESR continued to rise for four days, when it exceeded 110 mm. in one hour, then decreased during the next 10 days to a value of 32 on 1/14. In addition to the aortic diastolic and mitral systolic murmurs heard previously, a blowing, early diastolic apical murmur had appeared, as well as a presystolic apical murmur.

Cortisone, which had been reduced in dosage to 75 mg. a day, was discontinued on 1/19. Four days later her temperature began to rise, reaching 100 F. on 1/25. The evening of 1/24 she developed acute pain, swelling, heat and tenderness of the right wrist.

Cortisone was restarted on 1/25 at a dosage of 112.5 mg. per day. The next day pain and tenderness of both knees appeared. The ESR, which had been ranging from 40 to 49, rose to 72 on 1/25. The day after cortisone therapy was reinstituted her temperature had returned to normal. All joint manifestations had disappeared by 1/28. Her ESR continued to rise, however, to a value of 105 on 1/28. It then began to decrease at the same rate as when cortisone was first given, this time, however, reaching a lower value.

Her course since then has been one of steady improvement except for a mild "tightness" in her throat and enlarged sublingual glands which persisted from 2/3 to 2/15 in spite of penicillin therapy. She has been afebrile. Cortisone was gradually reduced in dosage until 2/20, when it was stopped.

Studies during this period included the following: three ECG tracings within normal limits; no glycosuria since cortisone was started; blood sugar levels normal on six occasions, and one at 121 mg. per 100 cc.; WBC gradually decreasing from 25,100 on 12/21/49 to 6,700 on 2/23/50; Hb rising from 7.2 Gm. on 12/29/49 to 11.3 Gm. on 2/14/50.

At this writing her convalescence is progressing satisfactorily. Physical examination shows the persistence of the apical systolic, diastolic, and presystolic murmurs and the aortic diastolic murmur. Ten days after cortisone was discontinued an abnormal ECG was recorded for the first time. The Q-T interval was prolonged and the T waves became flattened or diphasic.

4. J. K., a 14 year old white boy, was completing a five months' convalescence from a second episode of rheumatic fever when he contracted pharyngitis in late November, 1949. A week later there was a recurrence of rheumatic fever, characterized by repeated epistaxes, fever, dyspnea, and migratory joint pains. A screeching component appeared in the pre-existing apical systolic murmur, and the ESR rose from 12 to 90 mm. per hour. Because of the progressive anemia due to the profuse epistaxis, and his general downhill course, the patient was transferred from his convalescent home to a hospital, where blood transfusions were given.

In this hospital he was found to have, in addition to the cardiac findings mentioned above, an early diastolic apical murmur and basal rales. He was

suffering intensely from joint pains and was dyspneic enough to require oxygen therapy. Aspirin and penicillin were given without any improvement. The patient was transferred to the Philadelphia General Hospital on 12/19/49 for treatment with cortisone.

At this date the patient had been acutely ill for four weeks in his third attack of rheumatic fever. He was slightly dyspneic and orthopneic, and suffering repeated epistaxis, arthralgia and precordial pains. His temperature was 102.5 F. and his pulse rate was 120. He presented the murmurs characteristic of mitral insufficiency, mitral stenosis, and aortic insufficiency. His heart was enlarged. Laboratory studies were as follows: Hb: 8.0; WBC: 17,900; ESR: greater than 110; ECG: increased P-R interval.

Cortisone was started on 12/20/49 at a dose of 112.5 mg. per day. By 12/23 all joint manifestations had disappeared. However, the slowly descending temperature and ESR plus the relief of his arthritis were the only improvements noted at this time. On 12/22, two days after cortisone was initiated, his epistaxis recurred. On 12/23 his dyspnea and orthopnea became worse, he complained of severe precordial pain, a pericardial friction rub became audible, and an ECG confirmed the presence of pericarditis. Signs of heart failure appeared: his liver edge descended to 7 cm. below the costal margin and the rales at his lung bases became more obvious. Two days after cortisone therapy was begun the P-R interval was normal although the S-T segments were greatly elevated in the fashion characteristic of acute pericarditis. Auricular fibrillation was noted clinically and by ECG on one occasion (12/27).

By 1/4/50, 12 days after its onset, pericarditis had disappeared. At this date his ESR was 46 and his temperature 99 F. Premature beats were heard on 1/6, and on 1/7 auricular fibrillation recurred. He remained comfortable except for the dyspnea, however, until 1/8 when he developed acute pulmonary edema for which he was treated with oxygen, phlebotomy, and digitalization. After this episode he began a period of slow steady improvement. His heart reverted to a normal sinus rhythm, his ESR fell to 10, and there were no peripheral signs of heart failure. His cardiac findings were unchanged except for the appearance of a systolic thrill and murmur over the aortic area. The dosage of cortisone was reduced to 75 mg. a day on 1/11 and the drug was discontinued on 1/14 after 26 days. Digitalization was maintained.

The rheumatic process was considered to be subsiding in this patient until 1/23, nine days after cortisone was stopped, when he complained of pain in the left knee. During the next few days the other knee, one shoulder, and his chest became involved, the pain progressively becoming more severe. His temperature rose to 102 F., his pulse to 120 and his ESR to 70. His liver edge descended to 6 cm. below the right costal margin. The increased P-R interval reappeared.

Cortisone was restored on 1/24 at 75 mg. per day. The arthritic symptoms immediately began to recede, and the patient was free of pain by 1/27. His temperature reached its previous level by this day, and fell to normal three days later. His ESR fell from 70 on 1/28 to 21 on 2/1. The dyspnea improved sharply and by 2/3 had disappeared, although some orthopnea continued. An ECG on 2/14 showed a normal P-R interval, and, for the first time, an improvement in the T waves. The ESR fell to 7 on 2/8. Except for the improvement in cardiac compensation, there were no other cardiovascular changes. The dosage of cortisone was slowly decreased and the drug was discontinued on 2/20.

On 2/19, at which time the cortisone dosage was 1 mg. per day, the patient complained of a sore throat and his temperature was 100 F. orally. Headache, leg and shoulder pains, and earache developed over the next few days. The fever continued to rise, reaching 101.5 F. on 2/22. His ESR rose to 43 on the same day. A throat culture showed no recognized pathogens. Penicillin was given from 2/19 to 3/5. The temperature returned to normal after seven days of fever, the ESR reached normal limits in 14 days, and the Hb had risen to 13.8 on 2/14.

At this writing the disease process is apparently subsiding. The evidence or profound cardiac damage is still present, with the addition of an aortic systolic murmur and thrill. His electrocardiographic abnormalities are decreasing. He is continuing to receive digitalis.

Acknowledgment

We are indebted to Dr. Thomas M. McMillan for the readings of electrocardiograms which are summarized in this paper.

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Effect of Ascending an Ordinary Flight of Stairs on the Work of the Heart

Observations on Normal Individuals and on Patients with Coronary Heart Disease

By James A. L. Mathers, M.D., Harold I. Griffeath, M.D., Robert L. Levy, M.D., and John L. Nickerson, Ph.D.

Observations of cardiac work were made in normal persons and in patients with coronary heart disease after ascending an ordinary staircase at various rates of speed. Cardiac output was calculated from records obtained with the low frequency, critically-damped ballistocardiograph. The results were compared, for statistical significance, with those noted following descent and after walking for an equivalent distance on the level. It appears that the compensated coronary patient can mount a flight of stairs leisurely without imposing a greatly increased burden of work on the heart. The optimal rate of ascent usually is the one chosen by the individual.

IT IS common medical practice to advise patients with cardiac disease to avoid the use of stairs when feasible; in the presence of varying degrees of cardiac or coronary insufficiency many are cautioned against ascent at any time. It thus becomes necessary for these persons either to live on the ground floor or to resort to an elevator. Such arrangements may be difficult or impossible to make and frequently are a source of inconvenience and annoyance.

That mounting an ordinary flight of stairs places an added burden of work on the heart and circulation requires no demonstration. But the factors which determine the importance of such an effort for the patient with heart disease are unknown. What is the increment of increase? How does this compare with the changes observed after descending stairs or walking on level ground? What effect on the result have varying rates of performance? What is the duration of the changes in circulatory dynamics? What is their magnitude and duration in cardiac patients in comparison with those seen in normal individuals under similar conditions? These are some of the questions which must be answered if sound principles of guidance are to be followed.

This study is the first of a series in which such matters are to be considered. The present observations were made on normal persons and patients with coronary heart disease after performing various types of exercise on a staircase and walking on the level. It is planned to make similar studies in patients with other etiologic types of cardiovascular disease and also after other forms of effort, such as ascending a ramp.

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This investigation was carried out under a contract between the Army Research and Development Board, Office of the Surgeon General, and Columbia University, and was aided by a grant from the Division of Research Grants and Fellowships of the National Institutes of Health, U. S. Public Health Service.

Presented at the First International Cardiological Congress, Sept. 7, 1950, Paris, France.

Clinical Material and Procedure

Observations were made on 5 normal persons ranging in age from 41 to 77 years of age (average, 54.6 years), and in 5 patients with coronary heart disease ranging in age from 44 to 65 years (average, 55.2 years). Each group was composed of 4 men and 1 woman. Two of the patients had healed myocardial infarcts; one of them had been in congestive heart failure and was taking maintenance doses of digitoxin as well as a diet low in salt content. The diagnosis of coronary heart disease was confirmed in the other patients by the presence of a positive anoxemia test; in 2 of them, an electrocardiogram taken during a spontaneous attack of anginal pain showed alterations characteristic of acute coronary insufficiency.

A complete history was taken and a physical examination, electrocardiogram, 2 meter film of the heart and a hemoglobin estimation were made in each subject.

The observations consisted of the following: (1) determination of cardiac output four times at 3 minute intervals during a resting period and during the period of recovery after the exercise, at intervals of 1, 2, 3, 5, 7, 9, 12, 15, 20, 25 and 30 minutes; (2) recording of systolic and diastolic blood pressures and of heart rate at one minute intervals throughout. The cardiac output was calculated from records obtained with the use of the low frequency, critically-damped ballistocardiograph designed by Nickerson and Curtis[1] and tested by comparison with the direct Fick method by Nickerson, Warren and Brannon.[2] Lead II of the electrocardiogram was recorded simultaneously with the ballistocardiogram. The records were made without any attempt to control respiration. In the course of the work, more than 4000 ballistocardiograms were taken.

The exercises employed were of three types: (1) walking up one flight of stairs; (2) walking down one flight of stairs; (3) walking down the hall and back to the laboratory for an equivalent distance. All tests were carried out under basal conditions and after the subject had rested for 30 minutes in the recumbent position on an inflated air mattress on the ballistocardiographic table. Following the resting period, the subject was transported by wheelchair and elevator to the bottom or top of the staircase for the test of the day. The blood pressure cuff and electrocardiographic electrodes remained on the extremities during the exercise to facilitate the speed of making the observations during the recovery period. All obstructions, such as closed doors and other persons, were removed from the path of the subject being tested.

The three types of exercise were repeated twice at the individual's own chosen rate of performance. The effect of increasing or decreasing this rate was determined twice for each type of exercise in the 5 normal persons and in 3 of the cardiac patients. In no instance was more than one test given in the course of 24 hours.

The staircase was of the conventional variety and was in the Medical School building. It consisted of 2 sections of 11 treads each separated by an 8 foot landing. Each tread measured 11 inches in width, with a rise of 7 inches. The distance from the first step to the ballistocardiographic table was 70 feet and from the last step to the table was 34 feet. The time elapsing between the conclusion of the exercise and the beginning of the observations on the table was less than 30 seconds.

A control maneuver was performed in duplicate during which the same observations were made as already described. However, instead of performing the exercise, the subject was transported by wheelchair and elevator up or down one floor and returned to the ballistocardiograph without leaving the chair. He then stood erect for 30 seconds before resuming the recumbent position on the table. In this way the effects of all factors minus the prescribed exercises, could be determined.

The cardiac work was calculated according to the formula

$$CW = CO \times MP$$

where CW = cardiac work, CO = cardiac output (liters per minute), and MP = mean pressure (diastolic blood pressure + $\frac{1}{3}$ pulse pressure, in mm. Hg).

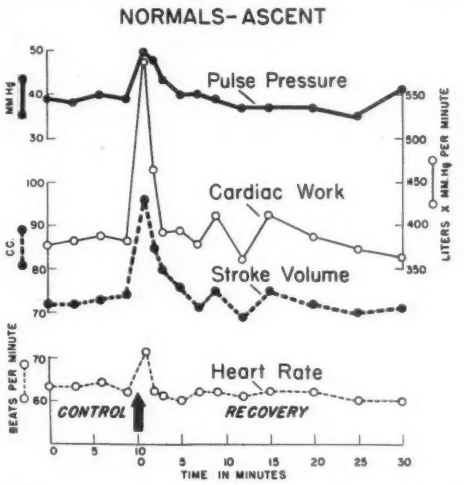

FIG. 1. Averages of changes in circulatory dynamics in 5 normal persons after ascending a flight of stairs at each individual's own chosen rate. Arrow marks ascent.

RESULTS

These are shown in figures 1 to 6. They are expressed as averages for the various groups under consideration; the figures have been submitted to statistical analysis.* It is clear that, although the number of observations runs into thousands, the number of subjects is relatively small. In order that the changes associated with exercise shall be of significant magnitude it is necessary that they should be comparatively large so as to cover the great variations within individual performances as well as varia-

* Dr. John W. Fertig, Professor of Biostatistics, School of Hygiene and Public Health of the College of Physicians and Surgeons, Columbia University, furnished helpful advice in making the statistical analyses.

tions between individuals. When significant differences are apparent they are of importance; when the differences are not significant although

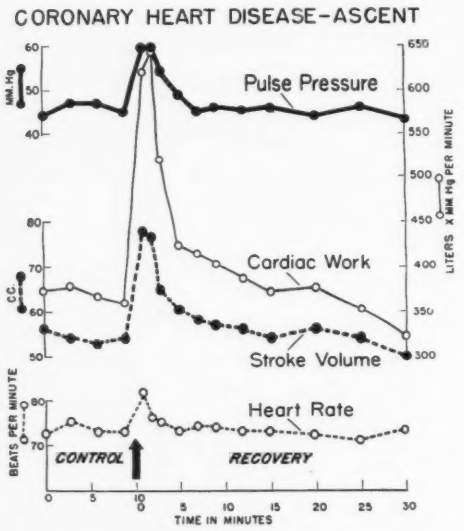

FIG. 2. Averages of changes in circulatory dynamics in 5 patients with coronary heart disease after ascending a flight of stairs at each individual's own chosen rate. Arrow marks ascent.

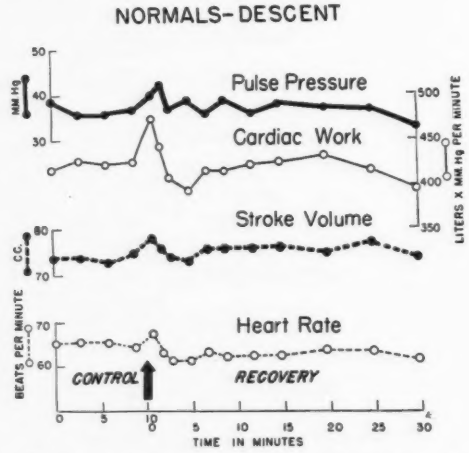

FIG. 3. Averages of changes in circulatory dynamics in 5 normal persons after descending a flight of stairs at each individual's own chosen rate. Arrow marks descent.

manifest, the lack of significance cannot be stressed, for negative conclusions might not be verified in a larger experience. In a few instances, borderline values were obtained and attention will be called to them in the proper

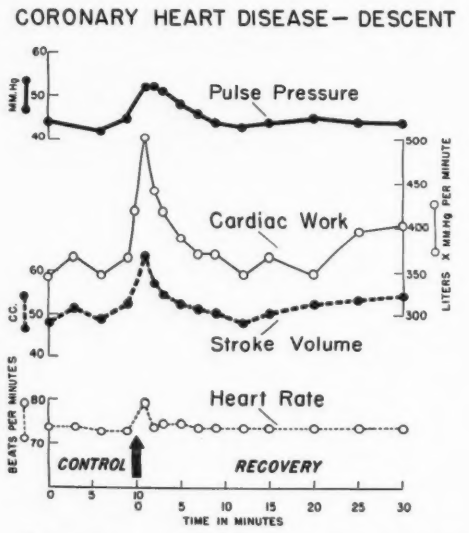

FIG. 4. Averages of changes in circulatory dynamics in 5 patients with coronary heart disease after descending a flight of stairs at each individual's own chosen rate. Arrow marks descent.

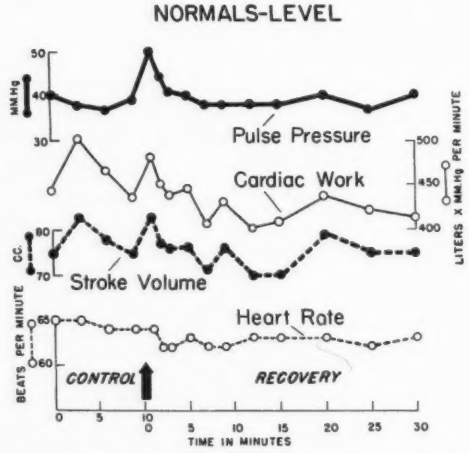

FIG. 5. Averages of changes in circulatory dynamics in 5 normal persons after walking on the level at each individual's own chosen rate. Arrow marks the walk.

places. For each group the changes are expressed as increases over the levels observed in the resting period for that particular group;

by so doing, the effects of the exercise alone are measured.

Ascent of Stairs. In the *normal subjects*, there occurred a significant increase in cardiac work, stroke volume and heart rate. The cardiac work increased 226 units* (54 per cent), the stroke volume 26 cc. (32 per cent) and the heart rate 8 beats (13 per cent). In the *patients with coronary heart disease* there was a significant increase in pulse pressure, cardiac work and stroke volume. The pulse pressure rose 18 mm. Hg (27 per cent), the cardiac work increased 323 units (75 per cent) and the stroke volume 30 cc. (44 per cent). The change in heart rate was small, with an average increase of only 9 beats per minute; this amount is not statistically significant.

The notable increases occurred in cardiac work and, to a somewhat lesser degree, in stroke volume in both normal subjects and cardiac patients. The changes were greater in the cardiac group but the differences between the two groups were not larger than might have been caused by chance variation.

Descent of Stairs. Although there were increases in the figures obtained for all four factors observed, these were not statistically significant in either the normal or the cardiac group; nor were there significant differences between the two groups. It should be noted, however, that in the normal group cardiac work increased 56 units (12 per cent) and in the cardiac group it increased 148 units (42 per cent). Similarly, in the normals, the stroke volume increased 5 cc. (2 per cent) and in the cardiacs 12 cc. (26 per cent). The increases were thus consistently greater in the cardiac group.

Walking on Level Ground. In the normal group, there was a borderline increase in pulse pressure and in the cardiac group, a similarly equivocal increase in stroke volume. The changes were not striking, either by themselves or on comparison of the differences between the two groups.

Control Maneuver. There were no significant increases in either group in any of the circulatory factors measured, nor were there noteworthy differences between the two groups. The changes throughout were numerically relatively small.

Varying the Rate of Performance of the Exercises. The chosen rate of speed of carrying out ascent, for the normals, was, on the average 29.6 seconds, with a range of 25 to 37; for the cardiacs, the average was 36.4 seconds with a range of 25 to 47. For descent, the average time for the normals was 26.7 seconds, with a range of 19 to 34; for the cardiacs, it was 31.1 seconds with a range of 23 to 37. For walking on the level, the average for the normals was 33.4 seconds, with a range of 22 to 42; for the cardiacs, it was 37.3 seconds, with a range of 31 to 47. Deliberately increasing or decreasing the rate of performance approximately 20 to 60 per cent did not significantly alter the results.

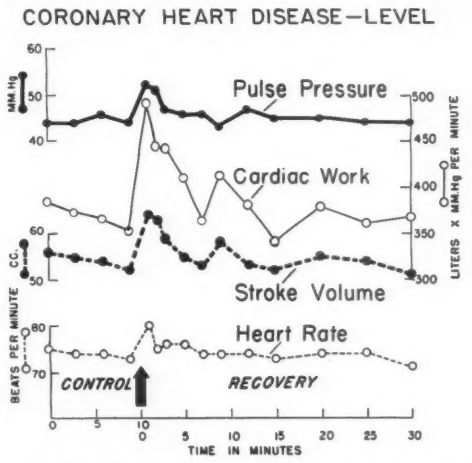

FIG. 6. Averages of changes in circulatory dynamics in 5 patients with coronary heart disease after walking on the level at each individual's own chosen rate. Arrow marks the walk.

For the normal group, in both ascent and descent, the individual's chosen rate of performance was the most rapid. At the request of the observer, the time was slowed down; the average slow rate was 47 seconds. For the cardiac group, the fastest average rate for ascent was 27.3 seconds; this was slowed, by request, in those whose original rate was faster than 30 seconds, to an average of 44 seconds; for de-

* The unit of cardiac work is obtained by multiplying the figure for cardiac output, in liters, by that for mean pressure, in mm. Hg.

scent, the fastest average rate was 26 seconds, which was slowed to 40 seconds for later observations. The normals, then, all slowed up by request; the cardiacs were less uniform in their chosen rates of performance and were asked to accelerate or retard as much as 20 per cent in either direction.

Although the average differences were not statistically significant, in most instances cardiac work was minimized when, in the ascent of stairs, both normals and cardiac patients were permitted to proceed without guidance. The individual, either as a result of habit or, in the case of the cardiacs, because of previous instruction, instinctively chose what for him was the optimal rate. Hickam and his group,[3] using both the Nickerson ballistocardiograph and the Fick method after cardiac catheterization, and Wolff and his associates,[4] using the same ballistocardiograph, have observed that ordinary physical exertions of everyday life performed during periods of relaxation impose little extra work on the heart, whereas, when carried out under emotional stress, they cause an increase in cardiac output. It appears from our experience that a conscious effort to modify the rate of performance of an exercise, even slightly, also may result in an augmentation of cardiac work.

Duration of Changes in Circulatory Dynamics after the Exercises. In the normal group the return to resting levels was completed at the end of the third minute during the period of recovery. The three-minute observation was chosen, therefore, as a reference point for measuring the duration of the increases noted. In the coronary group, after ascent, there was a significant delay beyond three minutes in the return to average resting values for cardiac work and a similar lag, of borderline significance, for stroke volume. However, in both instances, the delay was only a matter of a few minutes (fig. 2). There was no significant delay in the return to resting levels after the other exercises, in either group of subjects. In the normals, on descent and after walking on the level, there was a tendency for cardiac work to fall slightly below resting levels at the time of the three minute observation; this did not occur in the cardiac patients.

Discussion

Numerous studies have been made of cardiac output and cardiac work after effort, using a variety of methods.[5] For the most part, the exercises employed have been quite vigorous and have been performed at rates of speed fixed by the investigator. In the present study, the exercises used were moderate and, in the basic experiments, were carried out at a rate chosen by the individual subjects. Previous results and our own are not, therefore, strictly comparable. In addition, as far as can be determined, in no other study have statistical methods been applied to determine the significance of observed differences from control levels or of variations between normal individuals and patients with cardiovascular disease.

In this investigation, also, the usefulness of the low frequency, critically-damped ballistocardiograph has been demonstrated for making possible a large series of observations of cardiac output in each subject. The determinations of stroke volume and cardiac output were made on ballistic recordings taken without any constraint on the respiration. For some individuals with cardiac disease the ballistocardiographic patterns deviate from the normal form and the results for the stroke volume may differ somewhat from the absolute values. However, the relative changes in stroke volume are given quite accurately. The accuracy of the method for relative change was originally demonstrated by Nickerson, Warren and Brannon[2] and is further supported, in the present study, by the manner in which the curve for stroke volume parallels that for pulse pressure.

In dealing with group averages in a small series, it is inevitable that a wide range of individual variability will reduce the incidence of statistical significance of even comparatively large numerical differences between the groups considered. Under the conditions of these tests, it was observed that there was considerable individual variation.

The levels for the averages for cardiac work and for stroke volume during the resting period were lower for the cardiac group than for the normals in every series of comparisons. While

the difference was often considerable it cannot be termed significant in view of the large individual variations exhibited by both groups. Thus, although no symptoms or signs of congestive failure are present, the functional capacity of the heart, even at rest, apparently is somewhat diminished in patients with coronary heart disease. A similar observation was made by Starr and Wood,[6] using the ballistocardiographic method, and according to these observers, cardiac work, in the chronic form of this disorder, tends to decrease as the condition advances.

This study was undertaken primarily to obtain information of practical value in the guidance of patients with coronary heart disease with respect to the use of stairs. The inferences to be derived from our observations are somewhat at variance with current beliefs. It appears that ascending an ordinary flight of stairs at an individual's own chosen rate of speed, which is commonly a leisurely one, does result in a significant increase in the work of the heart. This is due chiefly to augmentation in cardiac output, since there is but little change in the heart rate. The differences between ascent on the one hand, and descent and walking on the level for an equivalent distance on the other, are in general, rather large numerically but are not, in all cases, statistically significant because of the individual variations. The amount of cardiac work observed in descent is, as might be anticipated, intermediate between that involved in ascent and that required for walking on the level. The absence of any notable increase in the rate of the heart following all three types of exercise, in both normal and cardiac groups, is also worthy of repeated mention. None of the 5 patients experienced discomfort of any sort during or following the tests performed in the course of this study.

Summary and Conclusions

In a series of 5 normal persons and 5 patients with coronary heart disease, observations were made after ascent of an ordinary flight of stairs, descent of these stairs and walking for an equivalent distance on the level. The low frequency, critically-damped ballistocardiograph was used to measure cardiac output. Cardiac work, stroke volume, pulse pressure and heart rate were recorded. The results were submitted to statistical analysis.

The ascent of stairs does not impose a greatly increased burden of work on the heart. The response of the patient with compensated coronary disease is not significantly greater, following this exercise, than after descent and is only slightly greater than after walking for an equivalent distance on the level. The stress is of relatively brief duration. Obviously, in the presence of congestive failure or if anginal pain occurs during the exertion, stairs should be avoided. Otherwise, the coronary patient may take them leisurely and preferably at a pace which he finds agreeable. Deliberate retardation, like hurry, may augment cardiac work.

Acknowledgments

For technical assistance the authors are indebted to Mr. Vincent Glaviano, Mrs. Bernadine Miller and Miss Isabella Clarke.

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Pathology of the Pulmonary Vascular Tree

II. The Occurrence in Mitral Insufficiency of Occlusive Pulmonary Vascular Lesions

By DONALD L. BECKER, M.D., HOWARD B. BURCHELL, M.D., AND JESSE E. EDWARDS, M.D.

Two cases of mitral insufficiency are reported. In 1 case the lesion was produced by rupture of the chordae tendineae of the posterior leaflet of the mitral valve. In the other case it was produced by fibrous adhesion of the posterior leaflet of the mitral valve to the underlying left ventricular wall, which occurred during healing of subacute bacterial endocarditis. Changes occurred in the pulmonary vascular bed which are essentially identical with those found in mitral stenosis.

IN 1936 Parker and Weiss[1] described certain changes which occurred in the pulmonary arteries and arterioles and in the alveolar walls in cases of severe mitral stenosis. These changes consisted of intimal thickening of arteries, hyperplastic arteriolosclerosis, arteriolonecrosis, collagenous thickening of alveolar walls, alveolar capillary dilatation, thickened capillary basement membranes, pericapillary edema and the presence of cuboidal epithelial cells lining the alveoli. In 1949 Larrabee, Parker and Edwards[2] confirmed these observations and stressed that medial muscular hypertrophy preceded intimal fibrous thickening of the involved vessels.

It is our purpose to present and discuss data on 2 cases of mitral insufficiency with pulmonary vascular changes identical with those seen in cases of mitral stenosis.

REPORT OF CASES

Case 1.

Clinical Features. A man aged 52 years entered the Mayo Clinic on Nov. 16, 1948, with chief complaints of weakness and dyspnea of 12 months' duration. In November, 1947, following a day's work on a harvesting combine, and while he was at rest, acute shortness of breath developed. For this he was confined to a hospital for one week. His condition improved slightly during the next two weeks, but he noted some weakness and returned to the hospital at the end of this time with "fluid in the lungs." He improved, but weakness continued. Subsequently palpitation and intermittent orthopnea developed. In April, 1948, edema of the lower extremities appeared. From September until the time of admission on Nov. 16 the symptoms became progressively more pronounced. One week before admission cough with blood-streaked sputum appeared. The patient had had frequent attacks of tonsillitis since childhood but had no other history suggestive of rheumatic fever or scarlatina.

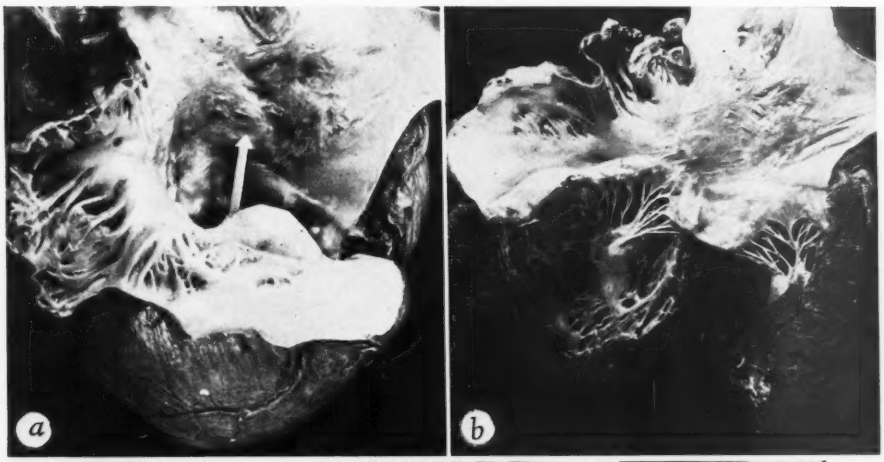
Examination revealed a white man, appearing chronically ill. He was dyspneic and was coughing. The apical beat of the heart was in the left axillary line. There was a loud, harsh systolic murmur with a presystolic component loudest at the apex. The murmurs were transmitted toward the left axilla. There were dry rales over the lower portion of the right lung, marked hepatomegaly and moderate pitting edema of the ankles. The blood pressure was 105 mm. Hg systolic, and 85 diastolic. The pulse rate was 106 beats per minute. Erythrocytes numbered 4,150,000 per cu. mm. of blood and leukocytes 14,100. The differential blood count was normal. The hemoglobin concentration was 12.2 Gm. per 100 cc. of blood.

The patient was treated with digitalis, diuretics and a diet low in sodium content. This resulted in an immediate loss of about 12 pounds (about 5 Kg.), with considerable improvement of his respiratory distress.

On December 1, 1948, a severe pain in the right flank suddenly developed, followed in five hours by a chill, a temperature of 104 F. and a friction rub in the right axilla. Roentgenograms of the thorax on the following day revealed evidence of consolidation in the right lower pulmonary field consistent with pulmonary infarction. A blood culture taken on December 2 was positive for hemolytic streptococcus. The patient's condition became rapidly more serious, with "spiking" fever, cyanosis, weakness and falling blood pressure. A regimen of penicillin, dicumarol and oxygen was instituted, but he did not respond. He died on Dec. 8, 1948.

Necropsy Features. The heart was enlarged, weighing 555 Gm. Both ventricles appeared slightly di-

From the Mayo Foundation and Mayo Clinic, Rochester, Minn.



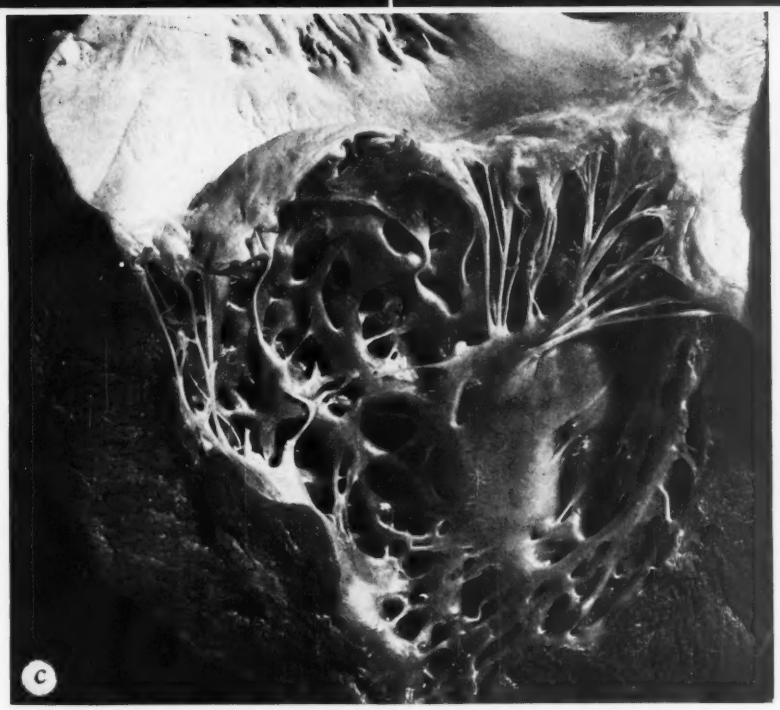


FIG. 1 (case 1). *a*. The left atrium from above. The posterior leaflet of the mitral valve has a dome-shaped deformity. The probe points to the endocardial "jet lesions" resulting from mitral insufficiency. *b*. The left atrium and left ventricle. The majority of the chordae tendineae of the posterior leaflet of the mitral valve (at the left side of the photograph) are ruptured. The endocardial "jet lesions" are seen on the left atrial wall. The left ventricular wall is hypertrophied. *c*. Posterior mitral leaflet showing details of ruptured chordae tendineae.

lated, and the ventricular walls were thickened, the left averaging 1.8 cm. and the right 1.0 cm. in thickness. The posterior leaflet of the mitral valve was distorted, bulging upward toward the left atrial cavity, and all of the chordae tendineae of this leaflet except three attached near the medial commissure were discontinuous (fig. 1*a* and *b*). The free ends of the disrupted chordae tendineae were

rounded and smooth (fig. 1*c*). Attempted approximation of the ends of the divided chordae revealed a deficiency of length averaging several millimeters. There was no apparent thickening of the involved chordae nor of the chordae tendineae of the anterior leaflet of the mitral valve. There were no vegetations on either mitral leaflet and the endocardial surfaces appeared normal. The circumference of the mitral valve was abnormally great (15.0 cm.), equaling that of the tricuspid valve. The endocardium of the inferior portion of the septal wall of the left atrium over an area 3 cm. in diameter was roughened and irregular and contained innumerable small elevations giving it a corrugated appearance (fig. 1*a*). There were multiple friable, thrombotic masses attached loosely to the wall of the right auricular appendage. The tricuspid, aortic and pulmonary valves were normal. The coronary arteries showed only minimal degrees of atherosclerosis.

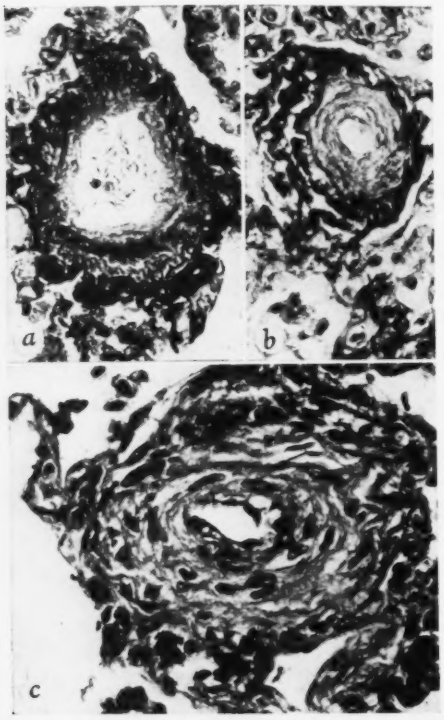


FIG. 2 (case 1). Pulmonary arterioles. *a*. Moderate collagenous intimal thickening causing narrowing of the lumen (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain. Reduced from ×435). *b*. Marked thickening of the intima by relatively acellular connective tissue. The lumen is very narrow (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain. Reduced from ×435). *c*. Marked cellular proliferation of the intima with great narrowing of the lumen (hematoxylin and eosin. Reduced from ×435).

The left lung weighed 430 Gm. It was crepitant and appeared slightly darker than normal, having a faint brownish hue. The right lung weighed 810 Gm. Deep within the substance of its upper lobe was a dark red circumscribed area of consolidation 2 cm. in diameter; a small pulmonary artery adjacent to this area was occluded by a dark red, moderately soft thrombus. The surrounding substance of the upper lobe of the right lung and the entire middle lobe appeared grossly normal. The central part of the lower lobe of the right lung was occupied by a firm, grayish, consolidated lesion 11 by 5 by 4 cm. in dimension. In the center it was softened as though necrotic. Two of the larger arteries supplying the region of the lesion were occluded by a yellow-brown adherent thrombus.

The main branches of both pulmonary arteries contained scattered yellow atheromatous lesions from 1 to 5 mm. in diameter.

The liver and spleen presented the gross picture of mild chronic passive congestion, weighing respectively 1,845 Gm. and 295 Gm. At the lower pole of the right kidney there was a pyramidal scar 0.5 cm. wide at its cortical base representing a healed infarct. The remaining organs appeared essentially normal.

Microscopically, sections of the myocardium from all chambers showed changes only in the left posterior papillary muscle. Here there were scattered tiny collagenous scars, each of a diameter only slightly more than the diameter of a muscle fiber.

Sections of two of the ruptured chordae tendineae revealed no cellular infiltration, vascularity or other recognizable abnormality. This supported the opinion that the chordae had ruptured long before death and probably at the same time as the onset of the patient's illness about a year before his death. A section of the left atrium through the area of roughened endocardium revealed rather marked irregular endocardial thickening by collagen and scattered fibroblasts. This change was interpreted as a "jet lesion" or an "endocardial pocket," that is, a lesion resulting from the trauma of regurgitant blood.

Whereas the lesions observed in the major pulmonary arteries and in intrapulmonary elastic arteries were atheromatous in nature, the lesions within the smaller pulmonary vessels were nonatheromatous. They were similar to those seen in the lung in cases of mitral stenosis.

For descriptive purposes the changes in the pulmonary vascular tree will be divided into those of the capillaries, the arterioles, the muscular arteries, elastic arteries and the veins. The alveolar capillaries, particularly in the upper lobes, were dilated and tortuous and appeared to have slightly thickened

basement membranes. Here and there the capillary dilatation was marked to the extent that there was protrusion of the capillary into the alveolar space, with the production of so-called capillary aneurysms. In general there were fewer visibly patent capillaries in the lower lobes than in the upper; some areas in the lower lobes were, in fact, noticeably deficient in patent capillaries.

The arterioles showed, in virtually all areas of all lobes, some degree of fibrous intimal thickening. This was caused in some instances by relatively acellular and collagenous tissue (fig. 2*a* and *b*), in others by concentric layers of fibroblasts (fig. 2*c*). These changes were often extreme, resulting in marked narrowing of the lumen. No vessels showed hyaline or necrotic changes.

The smaller muscular arteries showed medial hypertrophy causing mild or moderate degrees of luminal narrowing (fig. 3*a*). Many of the smaller muscular arteries showed, as well, intimal nonatheromatous fibrous thickening (fig. 3*b*, *c* and *d*). When this change was present the luminal narrowing was accentuated. A few of the small muscular arteries presented split and reduplicated internal

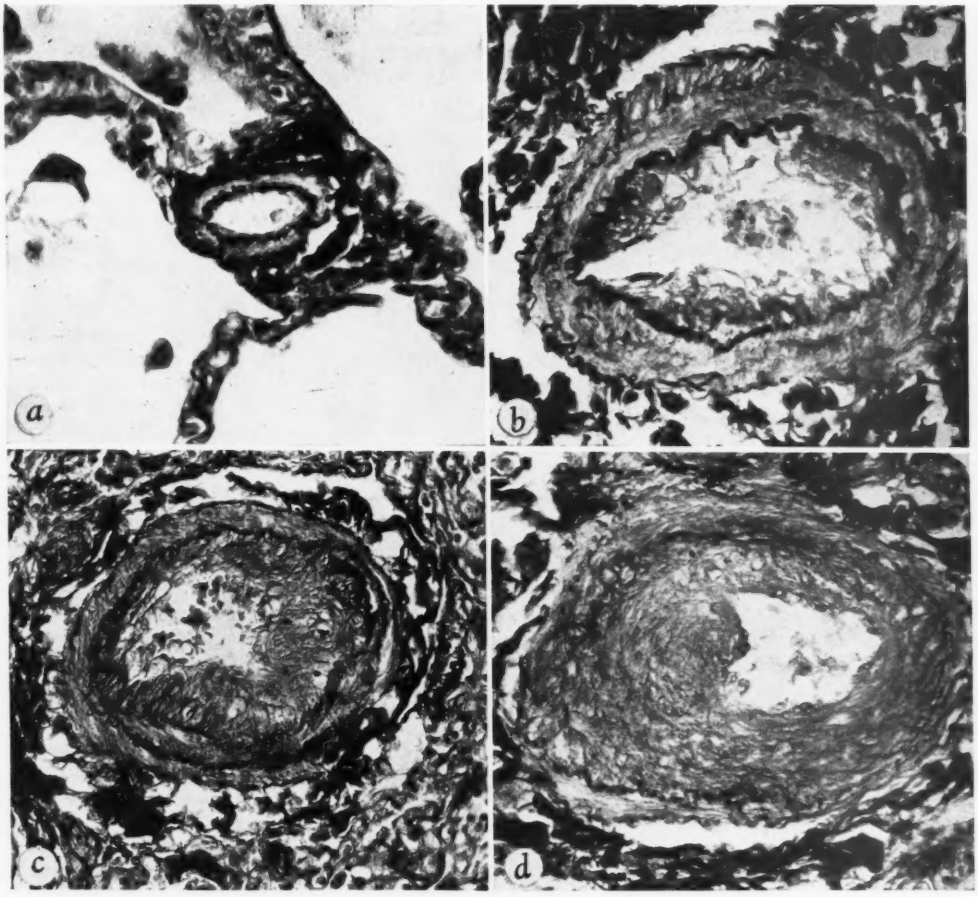


FIG. 3 (case 1). Pulmonary muscular arteries (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain). *a*. Small artery showing hypertrophy of the medial musculature with slight narrowing of the lumen. The intima is not thickened (×435). *b*. Medial hypertrophy and a moderate degree of intimal thickening (×350). *c*. Greatly narrowed lumen. The intimal thickening here overshadows the medial hypertrophy. Toward the right the media appears atrophic (×225). *d*. In this artery the intimal tissue is relatively acellular, dense and composed predominantly of collagen (×340).

elastic membranes. In some with pronounced intimal change, there was focal atrophy of the media (fig. 3*c*). In the larger muscular arteries the predominant change was muscular hypertrophy of the media. In a few vessels there were collagenous strands among the muscle cells. In nearly every vessel there was some degree of intimal thickening, although this was usually not a marked change. Almost every one of these vessels had some degree of narrowing of the lumen, usually slight in degree. The elastic arteries showed small focal intimal atheromas. The veins showed

FIG. 4 (case 1). Pulmonary vein showing irregular cellular thickening of the intima. The intimal tissue occurs in peculiar rounded bundles, and many of the cells resemble smooth muscle cells (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain ×165).

intimal thickening by bundles of smooth muscle and connective tissue (fig. 4).

In addition to the vascular changes described there were scattered pulmonary arteries of varying size containing organizing thrombi. The thrombi were interpreted as being emboli from the mural thrombus of the right auricular appendage.

In all lobes there were varying degrees of patchy alveolar collapse; the upper lobe of the left lung presented, in addition, areas of emphysema. The basement membranes of the alveolar capillaries appeared to be slightly thickened in the sections stained by the Masson trichrome stain, but this was by no means a marked change. In scattered areas in the lower lobes the alveolar epithelium was cuboidal in character; this change was seen only in the areas adjacent to infarcted pulmonary tissue. The alveolar spaces contained no precipitate resembling edema fluid. In all lobes there were scattered small extravasations of blood into the alveoli, and in every section numbers of macrophages laden with hemosiderin were seen. All of these changes were more marked in the lower lobes than in the upper lobes. The lumina of scattered bronchioles were filled with exudate, mainly neutrophils, accompanied by neutrophilic infiltration in the adjacent alveoli and connective tissue.

Case 2.

Clinical Features. A woman aged 43 years entered the clinic on Nov. 25, 1948, because of subacute bacterial endocarditis. Over a period of 20 years she had been repeatedly examined and treated at the clinic for rheumatic heart disease characterized by an apical systolic murmur and slight cardiac enlargement. Since childhood she had had a rather marked kyphoscoliosis. For eight years she had had intermittent episodes of mild congestive failure which responded well to the usual therapy. At the time of her admission she had a low-grade fever, splenomegaly, intermittent microscopic hematuria and recurrent tender red spots on the fingers. On November 29 an episode of abdominal pain developed, which was interpreted as resulting from splenic infarction. Blood cultures yielded *Streptococcus mitis.* Starting on Nov. 29, the patient was treated with penicillin in doses of 1,000,000 units daily for a period of 35 days. A blood culture taken two days after the beginning of therapy was negative. Many subsequent blood cultures were also consistently negative.

On Jan. 23, 1949, while the patient was at home after having felt quite well for a period of several weeks, acute severe right hemicranial headache suddenly developed, followed in a few moments by complete left-sided hemiplegia. During the following seven weeks the hemiplegia improved gradually to the point at which she was able to walk with assistance and to care for her own needs. Between June, 1949, and January, 1950, her condition remained stable. Her cardiac status seemed essentially the same as before her attack of subacute bacterial endocarditis.

Early in January, 1950, a cough developed, with mild dyspnea and orthopnea and edema of the feet. The patient's symptoms became gradually more severe. At the time of final admission on Jan. 27, 1950, the cardiac findings on physical examination were essentially like those of previous examinations. There were rales over the lower portions of both lungs. The liver was palpably enlarged and slightly tender. There were residual neurologic changes from the old left-sided hemiplegia. The patient was maintained on a regimen of digitalis, low sodium diet, mercurial diuretics and oxygen.

On Feb. 5, 1950, acute right-sided abdominal and right flank pain developed, associated with a low-grade fever. Respiratory distress increased, and the patient died on Feb. 7, 1950.

Necropsy Findings. The heart was enlarged, weighing 450 Gm. Both ventricles appeared dilated and the ventricular walls were thickened, the left averaging 1.7 cm. and the right 1.0 cm. in thickness. The central two thirds of the posterior leaflet of the mitral valve was firmly adherent to the underlying posterior wall of the left ventricle. This portion of the leaflet was completely immobilized and so had lost any ability to function as a valve flap. The anterior (aortic) leaflet of the mitral valve was slightly and uniformly thickened and contained a small calcified vegetation at the line of closure near the medial commissure. All of the chordae tendineae of the mitral valve were thickened and shortened. The circumference of the mitral valve was 12.5 cm. The endocardium of the inferior portion of the septal and posterior walls of the left atrium was roughened and irregular, presenting a corrugated appearance. The aortic, pulmonary and tricuspid valves appeared normal.

The right lung weighed 290 Gm. and the left, 255 Gm. The dependent portions of both lower lobes were firm, noncrepitant and dark red. The remaining portions of the lungs appeared normal.

The lining of the main branches of both pulmonary arteries contained a few scattered yellowish atheromatous plaques. The liver weighed 1,130 Gm. and presented the gross picture of mild chronic passive congestion. The right renal artery was completely occluded by a dark red thrombotic mass, and the right kidney was infarcted. There was marked kyphoscoliosis with rotation of thoracic and upper lumbar vertebrae to the left. Examination of the brain revealed an old cystic infarct in the right motor area.

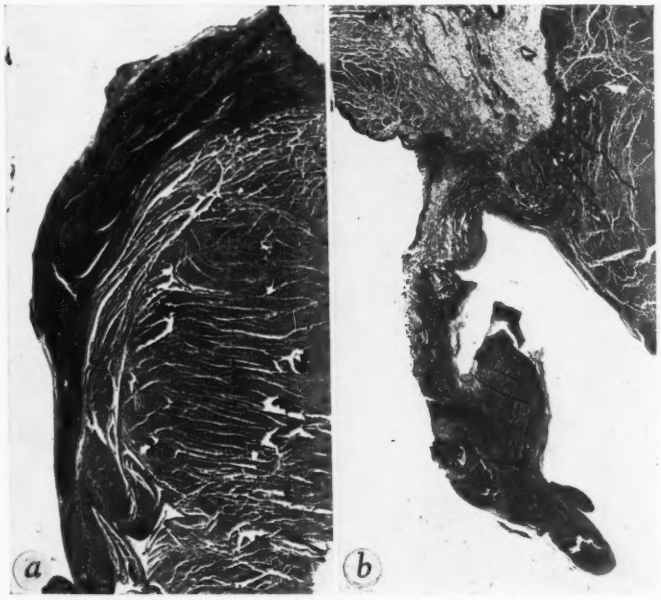


FIG. 5 (case 2). *a*. Longitudinal section through the central portion of the posterior leaflet of the mitral valve. This leaflet is fused with the endocardium of the underlying wall of the left ventricle by dense collagenous tissue (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain ×7). *b*. Longitudinal section through the anterior leaflet of the mitral valve immediately adjacent to the medial commissure. The left atrial wall lies above and to the left and the left ventricular wall to the right. This leaflet is thickened at the line of closure but is not abnormally adherent to the cardiac wall (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain ×7).

On microscopic examination the posterior leaflet of the mitral valve was applied closely to the surface of the underlying left ventricular wall and was bound so closely to it by bundles of collagenous connective tissue that it was difficult to distinguish ventricular endocardium from the valve proper (fig. 5*a*). Within the valve substance there were many small capillaries, and immediately adjacent to several of these were minute focal collections of neu-

trophilic leukocytes. At several points along the atrial aspect of the valve there was ulceration and small nodular excrescences of acellular fibrinous material.

At the line of closure of the anterior mitral leaflet there was a small nodular mass of relatively acellular collagenous connective tissue (fig. 5*b*). No infiltrating cells were present in the leaflet.

Representative sections of the myocardium revealed a small interstitial collection of lymphocytes in the ventricular septum. In the left anterior papillary muscle there were scattered small scars, consistent with healed small infarcts. No Aschoff bodies were identified in any of the sections.

Sections of the left atrium in the region of the corrugated patch revealed the irregular endocardial thickening by fibroblasts and collagen fibers of a jet lesion similar to that seen in case 1.

The lungs presented a picture almost identical to that of case 1 save that in case 2 there were neither major arterial occlusions nor infarcts. The capillaries were engorged and dilated in scattered areas of

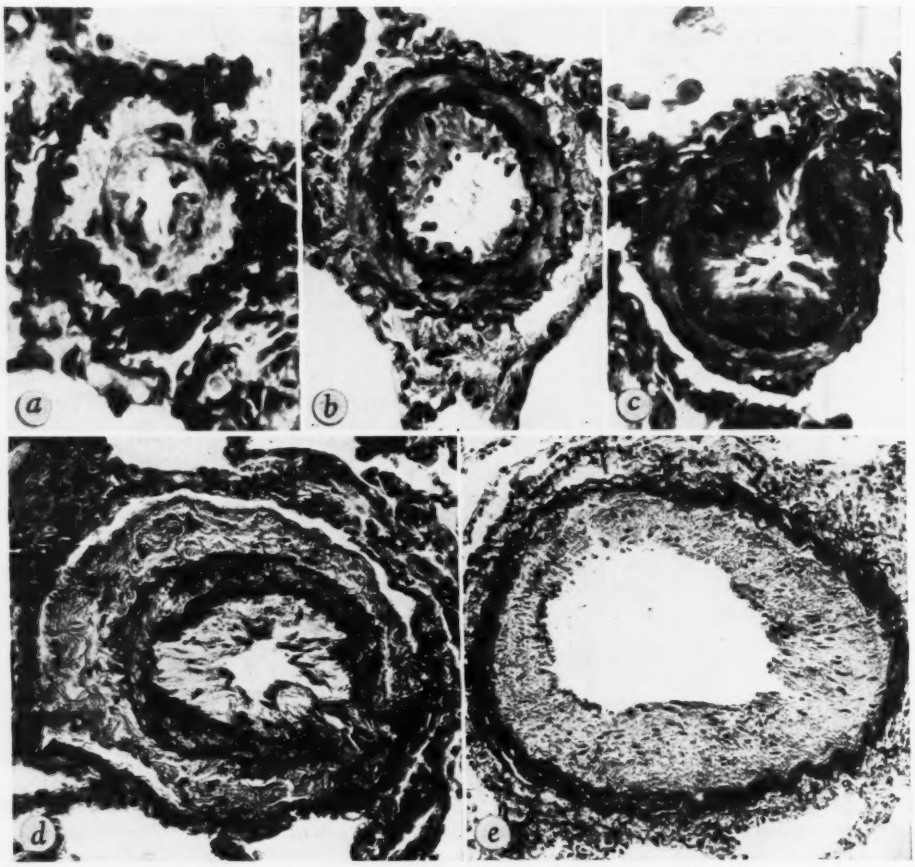


FIG. 6 (case 2). Pulmonary vessels (Verhoeff's elastic tissue stain counterstained with van Gieson's connective tissue stain). *a*. An arteriole showing marked intimal thickening by relatively acellular connective tissue. The lumen is very narrow (×515). *b*. A muscular artery showing muscular hypertrophy of the media and eccentric proliferation of the intima (×380). *c*. A muscular artery showing very marked luminal narrowing. The intimal proliferative change here overshadows the hypertrophy of the media. The intimal tissue is dense and acellular (×400). *d*. In this muscular artery the intimal tissue is cellular. The media is irregular in thickness and contains strands of proliferated elastic tissue. The adventitia is somewhat thickened by fibrous tissue (×250). *e*. A small vein. There is marked intimal thickening by fibrous tissue (×175).

all sections and there were many minute alveolar hemorrhages. The capillary basement membranes did not appear to be greatly, if at all, thickened.

The intimas of the arterioles were greatly thickened, in part by concentric cellular proliferation, but predominantly by collagenous fibers (fig. 6*a*).

The predominant change in the muscular arteries, present in virtually every vessel, was muscular hypertrophy of the mediae (fig. 6*b*). In some vessels there were collagen strands among the muscle cells. The smaller muscular arteries presented, in addition, varying degrees of cellular intimal thickening (fig. 6*c* and *d*). This change tended to occur much less frequently in the larger arteries of this type than in the smaller arteries.

The intrapulmonary veins showed intimal thickening with bundles of fibrous tissue (fig. 6*e*). Focal small atheromas were present in the elastic arteries.

Occasional small muscular arteries were partially or completely occluded by small organizing or organized thrombi. Throughout all areas of the lungs the alveoli contained numbers of hemosiderin-laden macrophages. Sections from the consolidated dependent portions of the lower lobes of both lungs revealed the picture of atelectasis. There was no evidence of alveolar edema fluid nor of acute inflammation. We were unable to find any areas in which the alveolar lining cells appeared cuboidal.

The spleen and liver presented moderate degrees of passive congestion. The right renal artery was completely occluded by a bland thrombus. No local or embolic source for this could be determined. Scattered glomeruli in the left kidney contained small adhesions between the capillary loops and Bowman's capsule. The blood vessels of the left kidney appeared normal; there was no evidence of hypertensive vascular changes in the vessels of the left kidney nor of any other area.

Comment

These 2 cases have in common a functional cardiac defect in the form of mitral insufficiency. The cause of each lesion is different; yet the end result has been almost complete inadequacy of the posterior leaflet of the mitral valve.

In case 1 mitral insufficiency resulted from rupture of the majority of the chordae tendineae of the posterior leaflet of the mitral valve. It is probable that rupture occurred immediately before the onset of symptoms about one year before the patient's death. Cause of the rupture has not been settled, but there is no evidence to support an inflammatory basis for it.

In case 2 there is evidence in the history and in the necropsy findings of chronic rheumatic mitral endocarditis without stenosis. As a complication of this in November, 1948, subacute bacterial endocarditis involving the mitral valve developed. Our interpretation is that with chemotherapy the mitral lesions healed and part of the posterior mitral leaflet became fused to the left ventricle, making it ineffective as a valve leaflet. This led to mitral insufficiency which probably existed for about thirteen months immediately before the patient's death. It was not felt that the kyphoscoliosis had had any significant adverse effect on her condition since it had existed since childhood.

It is to be emphasized that in our case 1 there was no evidence of valvular disease other than the rupture of chordae tendineae of the posterior mitral leaflet and the attendant effects of mitral insufficiency.

Bailey and Hickam[3] described 7 cases of ruptured chordae tendineae of the mitral valve. In 2 there was definite evidence of pre-existing rheumatic fever while in the remainder the changes suggested quiescent rheumatic fever but were not pathognomonic.

In our second case the rheumatic residue did not cause mitral stenosis. Mitral insufficiency therefore was the only functional valvular abnormality in each case.

We wish to focus attention on the fact that in each of our 2 cases of mitral insufficiency the hypertrophic and occlusive lesions in the pulmonary arteries, arterioles and veins were indistinguishable from those occurring in mitral stenosis.

Minor differences between our 2 cases of mitral insufficiency on one hand and the reported cases of mitral stenosis on the other were observed in the basement membranes of the alveolar capillaries and in the lining of the alveoli. We observed little, if any, thickening of the basement membranes of the alveolar capillaries; in mitral stenosis they may be thickened. We observed cuboid cells lining the alveolar walls only in relation to infarcts of the lung. In mitral stenosis these cellular changes need have no such localization.

With interest in surgical therapy of mitral stenosis becoming progressively greater and more widespread our cases seem to support the

concept that operative procedures on the stenotic mitral valve must be directed in such a way as to avoid significant mitral insufficiency. Otherwise secondary effects upon the pulmonary vascular tree and upon the right side of the heart may be caused or accentuated by the very operative procedures designed to prevent their occurrence.

Summary

Two cases of mitral insufficiency are reported. In one case the lesion was produced by rupture of the chordae tendineae of the posterior leaflet of the mitral valve. In the other case it was produced by fibrous adhesion of the posterior leaflet of the mitral valve to the underlying left ventricular wall, which occurred during healing of subacute bacterial endocarditis. Changes occurred in the pulmonary vascular bed which are essentially identical with those found in mitral stenosis.

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Controlled Myocardial Injury Produced by a Hypothermal Method

By C. Bruce Taylor, M.D., C. B. Davis, Jr., M.D., Gordon F. Vawter, M.D., and George M. Hass, M.D.

Following a review of experimental methods used for the production of necrosis or inactivation of the myocardium, a new method employing low temperatures is described. Lesions, with complete necrosis of muscle cells, can be controlled as to size and can be selectively placed to involve any of the four cardiac chambers and the interventricular septum. This facilitates attempts to study chronic myocardial insufficiency in terms of quantity and location of damaged muscle. Also, it has been possible to produce disturbances in conduction by production of small interventricular septal lesions. Refined electrocardiographic analysis of the magnitude and location of ventricular lesions has not been possible.

THE EXPERIMENTAL production of anatomic and functional myocardial injury has become a useful technic in physiologic, pathologic and electrophysiologic studies of the heart. Necrosis or inactivation of portions of the myocardium has been produced by various methods. Methods used previously will be discussed and a new hypothermal method, having certain advantages, will be described. All procedures discussed are modifications of one of three methods for the production of necrosis or alteration of function of myocardium, namely: ischemic necrosis or injury, necrosis or alteration of function with physical agents and injury or alteration of function with chemical agents.

Historical Review

Experimental myocardial infarction was first attempted by Panum in 1862[1] by the injection of a mixture of oil, wax, tallow and lampblack into the aortas of dogs. His results were not conclusive. Samuelson in 1881[2] and later Fenoglio and Drogoul in 1888[3] described the production of myocardial necrosis, in acute experiments in dogs, by the ligation of major branches of the left coronary artery. In acute and chronic experiments, Kolster in 1893[4] ligated small branches of the anterior descending branch of the left coronary artery. Animals were kept for as long as 17 months after the production of lesions. Porter,[5] in 1896, reported a large series of acute experiments in which he ligated major branches of the left coronary artery, the right coronary artery and branches to the interventricular septum. In some experiments, he occluded orifices of the coronary arteries with a curved glass rod which was inserted into the aorta and sinus of Valsalva through a slit in the innominate artery.

Necrosis of the myocardium with a sclerosing chemical agent was first produced by Lohman[6] in 1908. This investigator used sponges saturated with formalin to kill right atrial and adjacent muscle cells in rabbits. He was able to inactivate the sinoauricular node without hemorrhage and without interference with the flow of blood through its normal channels. Other early investigators who reported the production of myocardial necrosis in experimental animals are: Miller and Matthews (1909)[7] who studied the value of digitalis and strophanthin after ligation of the circumflex branch of the left coronary artery, Kahn (1911)[8] who first observed a negative T wave in the electrocardiogram following the ligation of coronary arteries, and Smith (1918)[9] who reported electrocardiographic and postmortem studies on

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This work was supported by grants from the National Heart Institute, U. S. Public Health Service, the Otho S. A. Sprague Memorial Institute and the American Heart Association.

66 dogs after ligation of the right coronary artery and branches of the left coronary artery.

Production of Ischemic Necrosis or Injury

Ligation of Large Coronary Vessels

Ischemic necrosis of large areas of the heart by permanent and complete ligation of the right coronary artery or a major branch of the left coronary artery of dogs has been used by many investigators.[9-22] Temporary occlusion of major branches of the left coronary artery of dogs has been reported.[8, 23-27] This procedure has been used for electrocardiographic studies of early changes in the R-ST segment and T wave in epicardial leads.[26, 27] Bronson[24] studied hearts of dogs thirty days after periods of ischemia ranging from 30 minutes to 2 hours. Ischemic periods of 30 minutes produced small focal areas of fibrosis; periods of 2 hours produced large fibrous scars similar to those seen after coronary thrombosis in man. Partial occlusion of coronary arteries was produced in dogs by Blumgart and co-workers[28] by ligating the vessel with a wire, having a known diameter, within the ligature; after ligation the wire was removed. Myocardial necrosis following the ligation of the coronary sinus and other cardiac veins has been reported by Robertson.[29]

Ligation of the anterior descending branch of the left coronary artery of dogs has been used in the evaluation of drugs used clinically following myocardial infarction.[30-34] This technic was used to study the effect of a sympathectomy on the size of myocardial infarcts.[35, 36] A sympathectomy did not reduce the size of infarcts.

Ligation of Small Arteries

Ligation of the right coronary artery or a major branch of the left coronary artery of dogs often precipitates fatal ventricular fibrillation or death within 24 hours. Ligation of small secondary arteries[37-43] has obviated this complication and has been useful for the production of small myocardial infarcts for electrocardiographic studies.

Ligation of Nutrient Arteries to Certain Regions

Necrosis of certain portions or structures of the heart has been produced by ligation of their nutrient arteries. Cushing and associates[44] ligated all arteries to the right and/or left atrium in 22 dogs. Necrosis of atrial myocardium, particularly subendocardial fibers, was not complete. Electrocardiographic changes were absent in 12 of the animals, transient in 4 and permanent in 6. In acute experiments, Kahn[8] ligated the interventricular branch of the left coronary artery and demonstrated right bundle branch block within 5 minutes. Removal of the ligature resulted in the disappearance of abnormal conduction. Kisch,[45] using a perfused, isolated heart, reported the production of complete atrioventricular block following ligation of the left coronary artery. Normal conduction was restored by opening the left coronary artery and occluding the right coronary artery. Lauterbach[46] reported the production of right or left bundle branch block following the ligation of the interventricular septal artery. Barton and Greenwood[47] were unable to demonstrate a permanent disturbance in cardiac conduction following ligation of the septal artery in spite of gross and microscopic evidence of large septal infarcts. In one animal there was a temporary complete atrioventricular dissociation one day after ligation of the septal artery. This disappeared within 48 hours. Wilson[48] ligated the septal artery in 3 dogs. Large septal infarcts were described. Right bundle branch block was observed in all animals. One experiment was an acute experiment; two were terminated after 48 hours.

In attempts to produce failure of the right heart, Starr[49] ligated all branches of the right coronary artery leading to the right ventricle. A postmortem examination was reported as showing only partial infarction of the right ventricle. Landis and co-workers,[50] in an interesting study of failure of the right heart, ligated the right coronary artery in order to produce decompensation of the right ventricle. Since his experiments were acute and postmortem studies were not reported, the degree of necrosis of right ventricular myocardium is not known.

Embolic Occlusion of Vessels

The injection of particulate matter for embolic occlusion of coronary arteries has been

used by a number of investigators including Hamburger and associates[51] Herman and Decherd[52] and Roos and Smith.[53] Lycopodium spores in suspension were injected by Hamburger and co-workers. Herman and Decherd described an ingenious method for the production of myocardial necrosis with a minimum of surgical trauma. Myocardial infarction was produced by instilling a drop of mercury into a coronary artery through a cardiac catheter that had been inserted through the carotid artery and into the sinus of Valsalva.

Roos and Smith described the production of acute cardiac failure in 15 to 35 minutes in dogs by injection of a suspension of starch in saline into the left ventricle. The aorta was occluded just above the aortic cusps during and briefly after the injection of the suspension of starch. The animals died within 10 minutes after evidences of cardiac failure were observed. Embolization of the systemic circulation was not ruled out in their experiments. They reviewed other work on experimental heart failure.

Experimental Coronary Thrombosis

The production of coronary thrombosis, experimentally, has been reported by Hall, Ettinger and Banting.[54] They reported degenerative changes in coronary arteries of old and middle aged dogs after daily injections of acetylcholine iodide or acetylcholine bromide for one to eight months. Thrombosis of coronary arteries was observed in 2 old dogs receiving the drug. Control studies and the number of animals used in the experiment were not mentioned. This work was repeated by Horswell[55] who used larger doses of acetylcholine. Degenerative changes in the myocardium and coronary arteries were not found by this investigator. Prolonged electrical stimulation of the vagus nerve (Ettinger and coworkers[56] and Manning and associates[57]) produced no changes in coronary arteries and controversial changes in the myocardium. Vagal stimulation produced by daily injections of extracts of the posterior lobe of the pituitary gland for three months to four and one-half years failed to produce coronary thrombosis or myocardial degeneration (Ettinger and associates).[58] The above evidence suggests that stimulation of parasympathetic fibers to the heart and the administration of parasympatheticomimetic drugs probably do not produce significant changes in the myocardium and coronary arteries.

Necrosis or Alteration of Function of Myocardium Produced by Physical Agents

Hyperthermal Injury of Myocardium

Electrocautery has been used for the production of myocardial necrosis by a number of investigators.[44,59-61] Thomas and Harrison[62] and Starr[49] inactivated portions of hearts with heated metal. Cushing and co-workers[44] reported atrial rupture within a few minutes after cauterization of the atria of dogs. In studies on cats, Crawford[61] found that complete penetration of the wall of the heart with electrocautery resulted in myocardial rupture within a short time. Most of the above investigators found hyperthermal injury satisfactory for only acute experiments unless precautions were taken to avoid complete penetration of the wall of the heart. Thomas and Harrison[62] produced hyperthermal injury of the left ventricle of rats for chronic experiments but a number of their animals died from rupture of the heart.

Injury of Myocardium from X-Ray

Irradiation from radon seeds (3 to 10 mc.) in a small glass capillary tube, has been used for the production of localized myocardial injury by Haney and associates.[63] The capillary glass tubes, containing radon seeds, were inserted into various locations in the ventricular myocardium of dogs. Lesions produced by this method had variable diameters ranging from 1 to 3 cm. It is of interest that frequently their animals died from a ruptured myocardium even after electrocardiograms indicated a healing myocardial infarct. Microscopic studies of the lesions were not reported.

Hypothermal Injury of Myocardium

Eppinger and Rothberger reported freezing local areas of the myocardium with an ethyl chloride spray.[64] Smith[65] briefly described the

application of test tubes, filled with hot and cold liquids, to the myocardium.

Hoff and Nahum[66] described the use of small (1 cm. diameter) metal thermodes cooled by circulating warm or cold water. The thermodes were placed on specific locations on the epicardium and endocardium. The endocardial thermode was attached to a 10 cm. plastic tube and apparently was inserted through the great vessels. The method of insertion of the endocardial thermode is not described. This technic was used in a study of the genesis of T-wave changes.

Myocardial Injury from Blows

Myocardial necrosis has been produced experimentally by striking the heart[67, 68] and the thorax with various instruments. These studies are related to traumatic injuries of the heart and will not be discussed further.

Surgical Myocardial Injury

Murray[69] has described surgical resection of infarcted left ventricular myocardium produced by ligation of the anterior descending branch of the left coronary artery. Resection of the infarcted myocardium resulted in a decreased incidence of fatal ventricular fibrillation following ligation of the anterior descending branch. Surgical extirpation of infarcted myocardium, which dilated during systole, resulted in an increased cardiac output and elevation of the blood pressure.

Barger, Richardson and Roe[70] have recently described a surgical technic for the production of chronic right-sided cardiac failure in dogs. Chronic right-sided cardiac failure occurred only in animals with surgically induced insufficiency of the tricuspid valve and stenosis of the pulmonary artery.

Injury or Alteration of Function of Myocardium Produced with Chemical Agents

Production of Myocardial Injury with Necrotizing Chemical Agents

It has been mentioned previously that Lohman[6] in 1908 first described the use of a necrotizing chemical for the production of myocardial necrosis. Hering[71] in 1909 also described the use of sponges saturated with formalin for the production of myocardial necrosis. Solutions of mercuric chloride (5 per cent) and silver nitrate (20 per cent) were injected into the myocardium by Eppinger and Rothberger.[64] They reported that the injection of silver nitrate (20 per cent) produced localized lesions which could be well outlined grossly and microscopically. The injection of mercuric chloride was not satisfactory. Smith[65] found that the injection of solutions of mercuric chloride and nitric acid was unsatisfactory because limiting the effects to definite portions of the myocardium was impossible. Otto,[72] who injected a 95 per cent solution of alcohol, also encountered difficulty in limiting lesions to certain areas. Others[44, 73-75] have described the use of necrotizing chemical agents for the production of myocardial necrosis in acute experiments. Cushing and co-workers,[44] using dogs, found that the application of solutions of phenol to the atrium resulted in death within one hour. Death was believed to have been due to the systemic, toxic effect of phenol. In general, the above investigators found necrotizing chemical agents useful for acute experiments. When chronic experiments were performed, ligation of nutrient vessels was usually the method used.

Production of Pericarditis with Chemical Agents

Although the technics described by Beck,[76] Armstrong[77] and Fishman and associates[78] are not methods for the production of myocardial injury, they are excellent methods for the production of right-sided chronic passive congestion. Beck and Armstrong injected irritating chemical solutions into the pericardial cavity. Fishman and co-workers inserted cellophane into the pericardial sac. Animals subjected to the above procedures developed progressive increases in venous pressure with chronic passive congestion of the liver, ascites and edema.

Chemical Agents that Disturb Cardiac Electrophysiology

During recent years the application of blotting paper saturated with potassium chloride (fifth molar) and other agents to the surface of the heart has been used for the

production of temporary disturbances in the electrophysiologic behavior of the surface of the heart.[79-90] Calcium chloride, strophanthin and ouabain produce similar effects. In 1920, Hoffman[79] described the use of blotting paper saturated with potassium chloride for the production of blocks in the atrioventricular conduction mechanism in isolated frogs' hearts. Later, Kisch[80, 81] described the use of this technic for the production of electrocardiographic changes (elevation of the S-T segment) in animals with the heart in situ. The changes produced were temporary and could be reversed by removal of the blotting paper saturated with potassium chloride. Reversal to a normal electrocardiographic pattern was hastened by washing the area affected with physiologic saline. It is of interest that Boyd and Scherf[90] were able to produce similar transitory disturbances in the electrophysiologic behavior of the heart with minimal mechanical stimulations of the surface of the heart. Kisch and associates[84] also reported similar disturbances following local applications of hot and cold objects. Hoff and Nahum[66] also described transitory alterations in the T wave following heating and cooling of the epicardium and endocardium with small metal thermodes. The work of Winkler, Hoff and Smith[91, 92] should be mentioned. These authors described electrocardiographic changes following the intravenous administration of calcium chloride and potassium chloride.

The technic to be described has merit as a method for the study of certain problems related to cardiac function. The apparatus and method will be described. Some results, obtained during development and early use of the technic, will be discussed. Its advantages and disadvantages will also be reviewed.

Apparatus

The hypothermal instrument used (figs. 1 and 2) is a modification of an instrument described by Hass and Taylor.[93] Myocardial injury is produced by creating a negative thermal gradient from the myocardium to the contiguous instrument which is cooled by expanding carbon dioxide.

The complete assembly has two functions. One function is the supply of carbon dioxide. The second function is the control of dimensions of myocardial lesions.

The supply of carbon dioxide is maintained in a standard commercial cylinder fitted with a pressure gage. The pressure in the cylinder is kept at 800–1100 pounds per square inch. A flexible metal hose, with standard fittings, connects the cylinder to the fitting at the base of the handle of the hypothermal instrument. When the instrument is assembled for use, one of the cooling plates, shown below the shaft of the instrument, is fitted to the end of the shaft. When the valve of the cylinder is opened, carbon dioxide passes through the flexible metal hose and through a small central tube in the handle and shaft of the instrument. The gas escapes through a small orifice at the

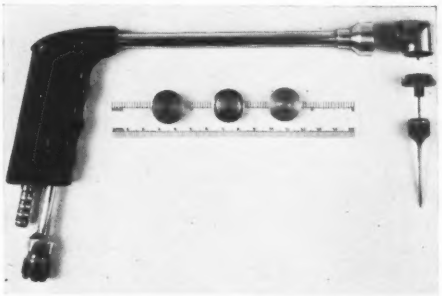

Fig. 1. Hypothermal instrument. The interchangeable cooling plates which have varied diameters lie on the ruler beside the shaft of the instrument. The right angle adaptor and hypothermal needle are shown below it.

Fig. 2. Trochar attachment for freezing instrument used in the production of interventricular septal lesions.

end of the shaft and expands opposite the inner surface of the cooling plate. Heat is abstracted from the plate and adjacent myocardium. The expanded gas escapes through eight peripheral holes at the end of the shaft and passes through the large external tube. It escapes through the orifice of the brass tube at the base of the handle.

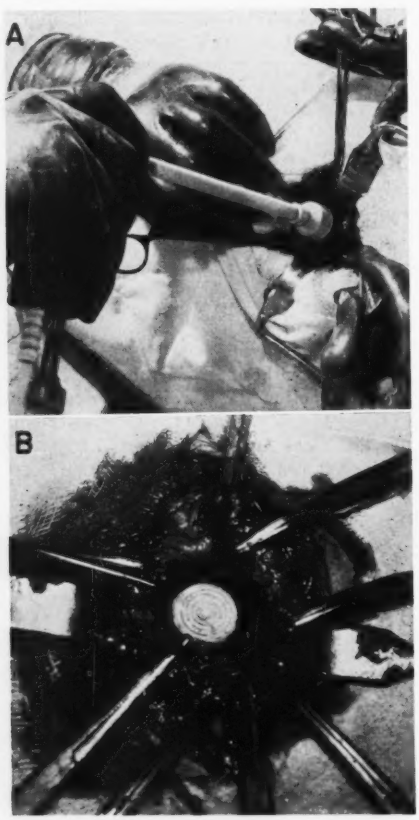

FIG. 3*A*. The hypothermal instrument in operation. The cooling plate is firmly frozen to the apex of the left ventricle. *B*. Myocardial lesion immediately following removal of cooling plate. The area frozen is a firm white cylindrical mass.

A right angle adaptor is illustrated in the lower right hand corner of figure 1. The adaptor is used in the production of posterior lesions in the atria and ventricles. Any one of the freezing plates can be fitted to the distal end of this adaptor.

A hypothermal needle is shown in figure 1. The needle consists of a larger external needle with a closed tip and a smaller internal needle. Carbon dioxide passes through the central needle, expands and escapes in the space between the external wall of the smaller needle and internal wall of the larger needle. It can be fitted to the hypothermal instrument and is used in the production of interventricular septal lesions. A trochar having a diameter of 5 mm. and a length of 13 cm. was also used (fig. 2). It operates like the needle described above.

The three freezing plates shown on the ruler in figure 1 have diameters of 6, 15 and 20 mm. respectively. They are interchangeable and are used to vary the diameters of lesions produced.

METHOD

General Procedure

Dogs weighing from 8 to 15 Kg. were anesthetized with Nembutal given intravenously (30 mg. per Kg.). An M.S.A. Pneophore* resuscitator was attached to an intratracheal catheter. The intratracheal catheter was made air tight by an inflated rubber cuff surrounding the distal end of the catheter. Intrapulmonic pressure was maintained at 10 to 15 mm. Hg.

Sterile surgical procedures were rigidly followed. The heart was approached through a parasternal incision or through an intercostal space. Either pleural cavity was approached on the appropriate side of the sternum. The costal cartilages were cut medial to the internal mammary vessels. In the dog there is a prominent subpleural muscular layer in the region of the sternum. This was cut across while entering a pleural cavity. Exposure of the heart was accomplished through different incisions in the pericardium. Incisions were purposely made away from the intended site of injury of the myocardium. The visceral pericardium was anesthetized by placing circular cotton pledgets saturated with 20 per cent Novocain over the site to be frozen. These pledgets were left in place for three minutes.

The tip of the hypothermal instrument was placed against the moistened surface of the heart at the desired location (fig. 3*A*). Large coronary arteries were avoided. The valve controlling the flow of carbon dioxide was opened. Carbon dioxide flowed through the instrument continuously. When a lesion of a desired depth was produced, the carbon dioxide was turned off. The instrument was heated by spraying steam through a needle into the exhaust outlet

*M.S.A. Pneophore, Mine Safety Appliances Co. Bradock, Thomas & Meade Sts., Pittsburgh 8, Pa.

of the instrument. This facilitated removal of the instrument from the heart within 30 seconds. Immediately following the production of a lesion the area frozen was a firm white cylindrical mass (fig. 3*B*).

After the production of the myocardial damage, the pericardial sac was closed with fine silk sutures. The chest wall was closed in layers. The costal cartilages were sutured with stainless steel wire. Postoperative pneumothorax was avoided by increasing intratracheal pressure to 30 mm. Hg as the chest was closed. The skin was closed with interrupted silk sutures.

When lesions were produced in the posterior walls of the ventricles and atria, the right-angle adaptor was used. Thus, the hypothermal plate could be readily placed against the posterior surface of the heart with minimal manipulation of the heart.

Serial electrocardiographic studies were made in 40 dogs with single myocardial lesions, in 2 animals with localized pericarditis produced by suturing a piece of cellophane (20 mm. diameter) to the epicardium and in 3 animals with massive myocardial lesions produced by making three or four confluent lesions. Serial electrocardiographic studies were also made in 4 control animals who were subjected to identical surgical procedures without producing myocardial lesions. Electrocardiograms were made before, during and 24 hours after the production of interventricular septal lesions. Standard leads I, II, and III and an apical precordial lead were taken serially in 27 animals with single myocardial lesions and in the 4 control animals. In 8 animals with single lesions the three standard limb leads and four precordial leads were taken (two on each side of the chest). In 5 animals with single lesions, 2 animals with localized pericarditis (produced with cellophane) and 3 animals with massive myocardial lesions, standard limb leads, unipolar limb leads and four or more unipolar precordial leads were recorded serially.

In a few animals, silver clips were placed in the centers of lesions. The lesions, easily identified with the aid of the silver clip, were studied fluoroscopically at frequent intervals during four weeks.

Dogs were sacrificed after variable periods of time ranging from 4 to 63 days. Hearts were weighed and fixed in formalin. The lesions were studied grossly and microscopically. Volumes of lesions were determined by measuring their areas and depths. The areas were determined by measuring a template having an area equal to that of the surface of the lesions. The depths of healed, retracted lesions were estimated by measuring the thickness of normal myocardium adjacent to the lesions.

Production of Interventricular Septal Lesions

Lesions were produced in the interventricular septum by two methods. The hypothermal needle was used in the production of discrete cylindrical lesions extending through the full thickness of the interventricular septum. The needle was inserted through the wall of the right ventricle and transversely through the septum. The course of the needle was guided by palpation through the thin, compressible, right ventricular wall. After insertion of the needle into the septum, lesions were produced by allowing carbon dioxide to flow through the instrument. Hemorrhage from the needle's puncture in the right ventricle was controlled by suturing a small piece of muscle over the wound.

Small, cylindrical, subendocardial lesions, having depths of 2 to 5 mm., were produced on the right surface of the interventricular septum by inserting a hypothermal trochar (diameter 5 mm.) into the right ventricle and placing the flat end of the instrument against a desired point on the septum (see fig. 2). Here again, the course of the instrument was guided by manual palpation through the right ventricular wall. Carbon dioxide was turned on until a lesion of a desired depth was produced. Electrocardiograms were recorded before surgery, after the chest was opened, after insertion of the freezing instrument into the right ventricle, during freezing of the septum and 10 minutes, 30 minutes, and 24 hours after septal injury.

Production of Multiple Right and Left Ventricular Lesions.

A large portion of the myocardium of either the left or right ventricle, excluding interventricular septal myocardium, was inactivated in two stages. The heart was approached through an anterolateral incision through the third or fourth intercostal space. The pericardium was opened in the usual manner. The epicardium was anesthetized by placing over the area to be frozen, for three minutes, a cotton pledget saturated with 20 per cent Novocain. Three or four transmural lesions having diameters of 20 to 25 mm. were produced at each operation. The posterior wall of the ventricle was attacked during the first operation. The anterior wall of the ventricle was damaged at the second operation. Pericardial adhesions over the lesions following the first operation presented no problem since in the case of two stage procedures the pericardial incision was made over the site to be frozen.

Quinidine (4 mg. per Kg.) given orally, one hour before surgery was used two times and seemed to be unsatisfactory for avoidance of fatalities when several myocardial lesions were produced. It successfully prevented ventricular fibrillation but animals died within 24 hours after surgery. A progressive bradycardia began during the production of lesions and terminated in cardiac arrest.

Instillation of 10 and 20 per cent Novocain into the pericardial sac was used during earlier experiments. This type of local anesthesia was later abandoned because it became apparent that not infrequently complete transmural right atrial anesthesia occurred resulting in fatal disturbances in cardiac conduction.

Results

Myocardial lesions have been produced in 87 dogs. Twenty-one dogs developed fatal ventricular fibrillation or cardiac arrest shortly after lesions were produced. Nine dogs died from infection of the pleura and pericardium; 57 animals survived. Mortality decreased progressively, as technics and methods were improved. Animals survived following the production of single or multiple lesions in the right or left ventricle and the interventricular septum. Lesions were produced in the posterior wall of the right atrium with survival. Animals were sacrificed 4 to 63 days after surgery.

Single lesions, having diameters of 15 or 20 mm. and, in most instances, being transmural, were produced in 36 animals with survival. Single lesions, with survival, were made anteriorly and posteriorly in the right and left ventricle and posteriorly in the right atrium.

Lesions were made in the interventricular septum in 12 dogs. Four dogs developed immediate fatal ventricular fibrillation. Four animals had lesions in the septum demonstrable at autopsy but had no disturbances in cardiac conduction. Four animals showed disturbances in conduction. One animal showed complete atrioventricular block. Three animals showed right bundle branch block. In one instance right bundle branch block was transitory, persisting for only a few minutes.

Multiple cardiac lesions were produced in 14 dogs. Two animals developed fatal ventricular fibrillation as lesions were being produced. In two experiments, with 40 mg. of quinidine given preoperatively, animals tolerated massive destruction of the right ventricle (one animal) and of the left (one animal), without developing ventricular fibrillation. However, in these 2 animals a progressive bradycardia with final cardiac arrest occurred in 1 and 24 hours, respectively. Ten animals survived with three or four transmural lesions in the right or left ventricle (without quinidine). Volumes of myocardial damage ranged from 27 to 50 per cent of the volume of right ventricle and 30 to 40 per cent of the left ventricle (excluding the interventricular septal muscle) (fig. 4). Two animals survived with six and seven lesions in the left ventricle and 2 animals survived with seven lesions in the right ventricle. The volume of myocardial damage was about 70 per cent in each case (excluding the interventricular septal muscle). In these 4 animals three or four lesions were produced at one operation; two weeks later three additional lesions were made in each animal.

Several factors were important in the control of fatal ventricular fibrillation. Anesthetization of the epicardium covering myocardium to be frozen was an important factor. The pledget saturated with Novocain was left on the epicardium for three minutes before a lesion was produced. Each area to be frozen was anesthetized before a lesion was produced. Manipulation of the heart was kept at a minimum and when necessary it was done gently. The production of sudden changes in the heart's position and filling pattern was hazardous after lesions had been produced. Nembutal given intravenously in doses greater than 30 mg. per Kg. was not desirable. Deeper anesthesia seemed to be a factor in the occurrence of ventricular fibrillation.

Fatal ventricular fibrillation was precipitated in a few instances by temporary occlusion of a major coronary artery. When proximal portions of the anterior descending branch or secondary descending branch of the left coronary artery were frozen, the flow of blood was temporarily occluded and ventricular fibrillation followed. Lesser branches were frozen frequently without fatalities. All epicardial vessels assumed normal function within a few minutes after the removal of the hypothermal instrument. Thrombosis did not occur in these vessels.

Ventricular fibrillation following the production of myocardial damage usually was irreversible and fatal. All animals with ventricular fibrillation were treated with manual cardiac massage and electric stimuli. One ampere of 110 volt current (Hooker and co-workers[94]) was passed transversely through the ventricles for from 0.2 to 1.0 second. Copper disks having diameters of 1 inch were placed securely against the lateral aspects of the ventricles. Frequently, electric stimulation was used five or six times in each case. Manual cardiac massage was used

between electric stimuli. One of 21 dogs survived longer than 12 hrs.; it was sacrificed 42 days after surgery. In this single instance ventricular fibrillation was corrected after having been present 20 minutes. Usually animals developed asystole within 30 or 45 minutes after the onset of ventricular fibrillation. Intracardiac injections of adrenaline, 1 cc. of 1:1000 solution, or intracardiac injections of Novocain, 2 cc. of a 10 per cent solution, were used in some instances with no apparent benefit. Hooker and his associates describe excellent results in correction of ventricular fibrillation by injecting 5 cc. to 10 cc. per pound of a solution containing calcium chloride, 0.046 per cent, in 0.9 per cent saline containing heparin and warmed to body temperature. They added 2 cc. of 1:1000 adrenaline to this mixture and injected it centrally into the carotid artery under a pressure of 150 mm. Hg. We did not use this method. It should be pointed out that Hooker and his co-workers corrected electrically induced ventricular fibrillation in hearts without myocardial damage. In all of the animals mentioned above, myocardial damage was present. In two experiments ventricular fibrillation occurred before myocardial damage was produced. This was corrected by electric shock.

The problem of postoperative pneumothorax was not encountered. Postoperative hydrothorax only occurred when infections occurred in the pleura. Pneumothorax was carefully avoided by increasing intratracheal pressure to 30 mm. Hg. as the chest wound was being closed. The wound was tightly closed simultaneously with an expiratory excursion of the chest.

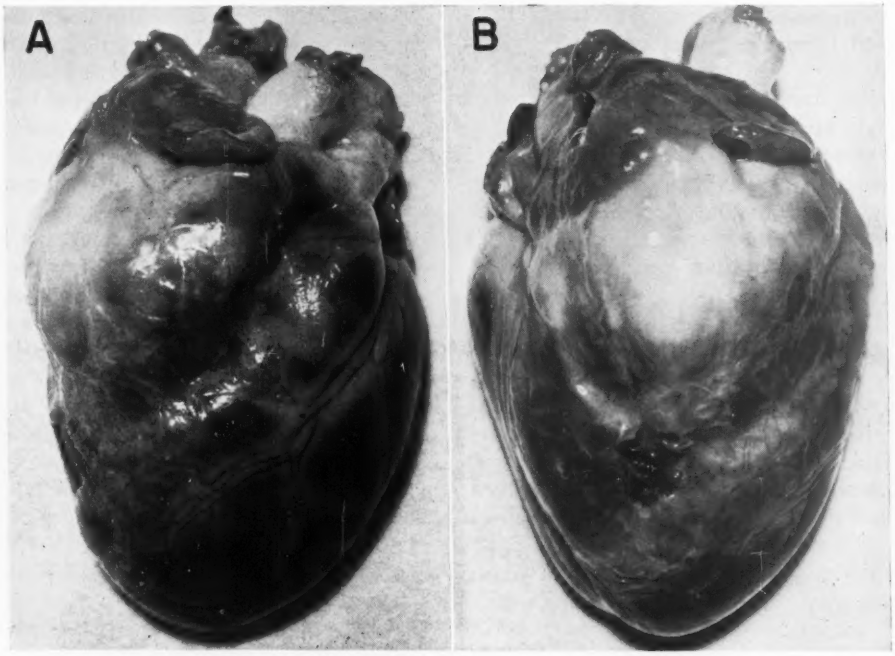

FIG. 4. Anterior view (*A*) and right lateral view (*B*) of a dog's heart showing multiple healed lesions in the right ventricle. Fifty-five per cent of the extraseptal myocardium of the right ventricle is replaced by a thin fibrous scar which in *A* shows some aneurysmal dilatation. In *B* the margin separating the thin scarred wall from normal myocardium can be seen.

Electrocardiographic Studies

Electrocardiographic studies were useful for the study of conduction disturbances during and after the production of interventricular

septal lesions. However, they were of practically no value for evaluation of age and volume of myocardial necrosis in the right or left ventricle. Lesions produced by this method invariably were accompanied by local areas of pericarditis which alone change the electrocardiogram. The two processes, myocardial necrosis and localized pericarditis, resulted in a mixed electrocardiographic picture. Only after subsidence of pericarditis (10 to 14 days) was localization at all feasible. Posterior and anterior myocardial lesions could usually be differentiated then. Finer localization was impossible.

Lesions were made in the posterior wall of the right atrium in 5 dogs. Two immediately developed fatal ventricular fibrillation. Two of 3 animals showed an inversion of the P wave through the eleventh postoperative day. The P wave had returned to normal (in one animal) on the twenty-ninth postoperative day.

Fluoroscopic Studies

Fluoroscopic studies showed paradoxic behavior of transmural myocardial lesions. During systole lesions showed mild aneurysmal dilatation. During diastole, since lesions were nonviable, there was no dilatation of lesions. Systolic aneurysmal dilatation was more marked during the first 14 days after myocardial injury. After fibrosis of lesions had occurred, dilatation during systole was less marked. These findings were more striking in animals with right ventricular lesions.

Pathologic Studies

Postmortem examination of animals, after myocardial damage had been produced, showed adherence of the pericardial sac to the line of closure of the healed thoracic surgical wound. Pleural adhesions were surprisingly minimal and consisted of a few fibrous bands between the anterior margin of the lung and the healed thoracic wound or the pericardium. Adhesions along the line of closure of the pericardial sac to the epicardium and from the surface of the lesion to the pericardial sac were a constant finding.

Immediately following the production of a lesion the area frozen was a firm white cylindric mass (fig. 3*B*). As the lesion thawed, vasodilatation became conspicuous in the epicardium and the myocardium. Widespread pericapillary hemorrhage and edema were present, but sharply limited by the boundaries of the lesion. Spontaneous hemostasis occurred promptly.

Cardiac lesions, a few hours old, showed a slight increase of edema and a mild fibrinous exudate on the epicardium overlying the inactivated myocardium. Microscopic examination showed a few agglutination thrombi in small blood vessels. The cells of cardiac muscle showed numerous minor structural alterations similar to those found in acute human myocardial infarcts. There were few infiltrating leukocytes. Fibrocytes, endothelial cells and collagen were surprisingly well preserved. No thrombi were found adjacent to the endocardium even when this structure was involved by the lesion.

The study of the evolution of the lesions showed progressive resorption of extravasated blood and degenerated cardiac muscle fibers. From the fourth through the fourteenth day calcium salts were present in degenerating cardiac muscle cells at the margins of lesions. These were apparently resorbed and were not seen in lesions older than 14 days (figs. 5 and 6). Fibroblasts and newly formed capillaries became conspicuous (fig. 6). Collagen was gradually deposited. There was never any suppuration, rupture of the myocardial wall or significant anatomic aneurysmal dilatation. A thin, contracted, depressed cylindric scar was the final result of healing (fig. 7). The principal difference at any stage between these lesions and human myocardial infarcts due to occlusion of coronary arteries was that the experimental lesions were always homogeneous and very sharply defined.

Discussion

The methods described have certain advantages over other methods for the production of myocardial injury. Complete necrosis of muscle fibers in a given area can be produced with certainty. Transmural lesions in any cardiac chamber can be made without danger of cardiac rupture, significant aneurysmal dilatation or intracardiac thrombosis. Myocardial necrosis can be selectively produced as to volume and location. Volumes of myocardial damage

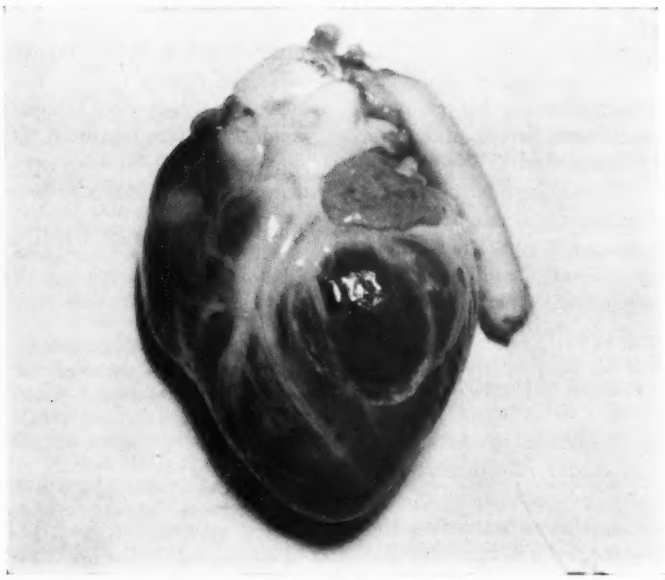

FIG. 5. A transmural anterior left ventricular lesion in a dog's heart. Calcium salts can be seen at the margins of the lesion which is one week old. The coronary vessel shown passing over the surface of the lesion was not thrombosed. It was frozen when the lesion was made. (*The use of color in this illustration has been made possible by a grant from Wyeth Incorporated to the publication fund of the American Heart Association.*)

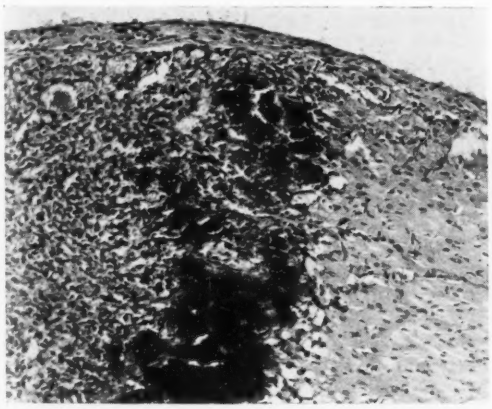

FIG. 6. Photomicrograph of margin of lesion shown in fig. 5. The masses of dark granular material separating the lesion from normal myocardium are calcium salts stained with hematoxylin. In the lesion there is complete necrosis of muscle cells. Fibroblasts and newly formed capillaries are conspicuous.

FIG. 7. A healed hypothermal lesion at the apex of the left ventricle of a dog's heart. The lesion, a transmural lesion produced by freezing the area two minutes, is six weeks old.

can be predicted quite accurately and can be measured accurately at postmortem examination. Large portions of the right or left ventricle can be inactivated by successive operations in chronic animal preparations. These animal preparations with massive destruction of a ven-

tricle are now being used in the study of chronic cardiac failure.

Discrete, small interventricular septal lesions, which are readily detectable at postmortem examination, were produced on the right side of the septum and could be produced on the left side with this method. In some cases disturbances in cardiac conduction were observed. Lesions produced by this method, with electrocardiographic studies, offer an excellent pathologic-physiologic method for the study of the cardiac conduction mechanism. The sinoauricular node could be approached through the posterior wall of the right atrium by this method.

The method has disadvantages. As the results indicate, the mortality rate in these experiments was high. However, most of the unsuccessful experiments occurred during the first half of the study. As technics improved the mortality rate decreased markedly. Local pericarditis at the site of myocardial lesions and the site of closure of the pericardial sac occurred regularly. The superimposition of electrocardiographic changes due to localized pericarditis upon those due to myocardial necrosis makes electrocardiographic studies difficult to interpret.

Summary

A method for the production of controlled myocardial injury in dogs has been described. Permanent inactivation of large or small quantities of myocardium was produced with an instrument cooled to −60 C. by expanding carbon dioxide. Transmural lesions were produced in any cardiac chamber, including the right atrium, without danger of rupture, aneurysmal dilatation or intracardiac thrombosis. Quantities of myocardial damage were predicted quite accurately and measured accurately post mortem. Necrosis of muscle cells was complete throughout the lesions produced. Large portions of the left or right ventricle were inactivated giving a chronic animal preparation suitable for study of cardiac failure.

Lesions produced by this method are unsatisfactory for refined electrocardiographic analysis of myocardial necrosis, because of interference incidental to pericarditis.

A method for the production of small discrete interventricular septal lesions with a cold needle has been described. The size and location of lesions was controlled. Disturbances in cardiac conduction were produced by this method. Lesions produced by this method were easily defined, grossly and microscopically.

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The Effect of "Sympatholytic" Drugs on the Cardiovascular Responses to Epinephrine and Norepinephrine in Man

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Under controlled conditions the effects of various "sympatholytic" agents on the cardiovascular responses to epinephrine and norepinephrine were compared in man. The dosages of the sympatholytic drugs administered approximated those usually employed clinically. Such basic data are given for the following agents: Dibenamine, the imidazoline derivatives [Priscoline and Regitine (C-7337)], the dihydrogenated alkaloids of ergot (D.H.K. and C.C.K.), L-hydrazinophthalazine (C-5968), tetraethylammonium, and hexamethonium (C6).

IN RECENT years a variety of agents have been introduced which inhibit the motor activities of the sympathetic nervous system. Determination of the mode of action of such drugs has not been clarified completely especially in man. According to Nickerson[1] "adrenergic blockade" refers only to compounds which specifically inhibit the responses of effector cells to both epinephrine and sympathetic nervous impulses. Thus, adrenergic blocking agents such as Dibenamine should be differentiated from drugs which inhibit transmission through the sympathetic nervous system either in the ganglia, such as tetraethylammonium[2] or the central nervous system, such as pentaquine,[3] but do not block the pressor effects of epinephrine.

The present investigation was designed to determine under controlled conditions the effects of the various "sympatholytic" drugs on the pressor responses to an excess of circulating epinephrine in man. In addition, it seemed of interest to test the effectiveness of such drugs in inhibiting the hypertension associated with an excess of circulating norepinephrine. This substance has assumed greater importance since it has been found in mammalian chromaffin tissues[4] and in human pheochromocytomas[5] and since the hypertension produced by norepinephrine in man resembles essential hypertension in many respects.[6] Finally, a systematic study in which various drugs are tested under identical conditions in doses customarily used clinically seemed worthwhile in order to supply basic data as to the comparative value of these compounds as adrenergic blocking agents in man.

MATERIALS AND METHODS

The subjects were young or middle-aged adult men admitted to the wards of the Veterans Administration Hospital, Washington, D. C. All were convalescing from nonfebrile illnesses at the time of testing and none exhibited cardiovascular abnormalities.

Commercial epinephrine in a concentration of 1 μg. per cc. in saline and norepinephrine in a concentration of 1.5 μg. per cc. were infused intravenously. The rate of infusion was controlled by an adjustable clamp and calibrated Murphy drip bulb. With the patient reclining in the supine position an infusion of isotonic saline was introduced through an antecubital vein. The needle used in this infusion was connected to a three way stopcock to permit introduction of the norepinephrine and epinephrine solutions as well as the blocking agents studied without disturbing the patient. The arterial pressure was measured in the opposite arm with an arm cuff and mercury manometer while the heart rate was counted at the wrist.

In the control period, after the arterial pressure

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Sponsored by the VA and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

The norepinephrine used in this study was generously supplied by Ciba Pharmaceutical Products, Summit, New Jersey.

and heart rate had become stabilized, the epinephrine solution was introduced through the three way stopcock and the rate of infusion regulated by adjusting the clamp of the Murphy drip. The responses of arterial pressure and heart rate were measured at both low and high infusion rates of epinephrine. Following these control determinations using epinephrine, the three way stopcock was turned so that saline was again infused. After the arterial pressure and heart rate had returned to basal values the norepinephrine infusion was connected and the responses to this agent measured at low and high infusion rates. It should be noted that the dose ranges of both epinephrine and norepinephrine were considerably lower in these studies on human subjects than the dosages of such substances usually employed in investigations in animals.

Following the control determinations the particular blocking agent under study was given through the intravenous tubing of the saline infusion following which epinephrine and norepinephrine again were infused at the same rates as had been administered during the control period. An exception to this procedure was used in testing the adrenergic blocking action of benzodioxane. Because of its fleeting action, this drug was given during the infusions of epinephrine and the dose was repeated again during the infusion of norepinephrine.

Results

Effect of Epinephrine and Norepinephrine Alone

At low infusion rates (below 0.10 μg. per Kg. per minute), epinephrine frequently resulted in a decrease rather than an increase in the mean [(systolic + diastolic)/2] arterial pressure. This was due primarily to a reduction in diastolic blood pressure although systolic pressure frequently was depressed as well. As the mean pressure fell, the cardiac rate increased. With higher infusion rates of epinephrine (0.10 microgram per Kg. per minute or above) the mean arterial pressure usually rose. This elevation was due to the fact that the percentage increase in systolic pressure was greater than the percentage decrease in diastolic pressure. However, there was considerable variation in response among different patients, some exhibiting very little depressor response, while others showed depressor responses exclusively even at the high infusion rates. Following cessation of the epinephrine infusion, the cardiovascular responses disappeared rather slowly over a period of 2 to 10 minutes.

In contrast, the responses to norepinephrine were uniform in all patients. Immediately following infusion of an effective dose (0.1 to 0.2 microgram per Kg. per minute) both the systolic and diastolic pressure rose and the heart rate decreased. These cardiovascular responses disappeared in one to three minutes after the infusion was discontinued.

Effects of Dibenamine

Dibenamine was administered to 4 subjects in doses of 170 to 360 mg. (2.3 to 6 mg. per Kg.). In every case the pressor responses to epinephrine were reversed even with doses of epinephrine as high as 0.5 microgram per Kg. per minute (table 1). The hypertension that resulted from the infusion of norepinephrine was 90 to 100 per cent abolished. In 2 subjects complete abolition occurred at low rates of norepinephrine infusion but not at high infusion rates. Nevertheless, marked inhibition of the norepinephrine hypertension occurred even at high infusion rates (0.5 to 1.0 μg. per Kg. per minute of norepinephrine).

Dibenamine tended to exaggerate the tachycardia which accompanied the infusion of epinephrine, while in 3 of the 4 cases it completely abolished the bradycardia that occurred during norepinephrine infusion.

Effect of Benzodioxane

Benzodioxane was administered to 3 subjects in doses of 10 to 20 mg. during the infusions of epinephrine and norepinephrine. Two subjects received 10 mg. intravenously during the infusion of epinephrine. No significant inhibition of the pressor response occurred although there was an increased tachycardia in one of the cases. These 2 subjects received an additional 10 mg. of benzodioxane during the norepinephrine infusion. Thirty-one and 54 per cent inhibition of the norepinephrine hypertension resulted. However, this inhibition was quite fleeting, lasting only one to two minutes.

The third subject (W. S.) received 20 mg. of benzodioxane during the infusion of epinephrine with resulting "reversal" which was of less extent and of much briefer duration (four minutes) than was observed in the subjects who received Dibenamine. An additional dose of 20

TABLE 1

Control										After Drug								
				Epinephrine			Norepinephrine					Epinephrine				Norepinephrine			
Pt.	Wt. Kg.	Arterial Pressure mm. Hg	Heart Rate/ min.	Dose Mg./ Kg/ min.	Change M.A.P.* %	Change Heart Rate %	Dose Mg/ Kg. min.	Change M.A.P.* %	Change Heart Rate %	Drug	Dose mg.	Dose Mg/ Kg/ min.	Change M.A.P. %	Reversal	Change Heart Rate %	Dose Mg/ Kg/ min.	Change M.A.P. %	Inhibition† %	Change Heart Rate %
S. T.	76	114/76	62	0.10	+20	+16	0.12	+20	−20	Dibenamine	170	0.10	− 7	+	+66	0.13	+ 2	90	−10
L. B.	84	120/60	92	0.10	+ 8	+13	0.10	+20	−18	"	350	0.10	−16	+	+ 8	0.15	0	100	0
				0.13	+13	+17	0.25	+33	−22	"		0.13	−16	+	+13	0.25	+ 3	91	0
A. S.	59	118/70	70	0.07	− 4	+ 9	0.23	+31	−26	"	350	0.085	−10	+	+53	0.23	+ 3	90	0
				0.10	− 6	+54													
W. S.	61	110/70	68	0.23	+ 8	+23	0.15	+11	−20	"	360	0.26	−15	+	+ 6	0.37	0	100	0
				0.33	+16	+ 5	0.18	+17	−20			0.50	−14	+	+24	0.68	+ 8		0
																1.01	+13		0
W.	61	110/60	70	0.20	+11	+31	0.35	+29	−9	Benzodioxane	10 + 10	0.20	+14	−	+31	0.20	+20	31	− 5
C. W.	69	110/70	70	0.09	+ 9	+13	0.15	+24	−10	"	10 + 10	0.09	+ 5	0	+39	0.15	+11	54	0
W. S.	61	120/80	70	0.15	+ 3	+29	0.10	+ 8	−23	"	+20	0.15	− 5	+	+48	0.10	+ 2	75	− 5
W.	61	110/60	70	0.08	+10	+28	0.22	+19	− 6	C6	50	0.08	+14	−	0	0.22	+20	0	−10
R. B.	65	118/78	72	0.16	−17	+ 5	0.20	+ 9	− 5	C6	35	0.16	0	−	+13	0.20	+52		−12
T. W.	61	130/60	100	0.10	0	+24	0.18	+14	− 4	C6	50	0.10	+ 7	−	+16	0.18	+28		− 8
C. W.	69	110/70	70	0.09	+ 9	+14	0.15	+14	−14	TEA	400	0.09	+12	−	−32	0.15	+31		−18
J. L.	64	100/68	68	0.14	− 3	+30	0.15	+14	−18	TEA	350	0.14	+ 6	−	+ 5	0.15	+26	0	−23
A. C.	80	118/72	64	0.08	+ 2	+31	0.26	+17	−22	Priscoline	25	0.08	− 6	+	+30	0.26	+ 7	60	−18
C. T.	70	125/70	80	0.07	− 6	+15	0.17	+14	−19	Priscoline	25	0.07	−16	+	+35	0.17	+19	0	− 7
											125					0.17	+ 7	50	−10
A. T.	65	125/74	60	0.09	0	+33				C-7337	25	0.09	− 8	+	+65				
							0.09	+17	−20	"	50					0.09	+ 4	76	+ 4
							0.14	+22	−20	"	50					0.14	+16	27	− 7
W. H.	57	112/60	60	0.10	+ 7	+17	0.20	+15	−13	"	25	0.10	− 5	+	+22	0.20	+ 7	53	−16
							0.45	+27	−23							0.45	+12	56	−16
S. P.	64	130/95	68	0.18	− 1	+30	0.15	+12	−14	"	50	0.18	−11	+	+42	0.15	+ 4	75	0
				0.24	+ 6	+28	0.23	+25	−24			0.24	−11	+	+42	0.23	+ 6	76	0
												0.34	−23	+	+89	0.52	+11	?	− 8
W. W.	48	105/60	68	0.12	+33	+37	0.28	+51	−24	C-5968	18	0.12	+12	−	+40	0.28	+45	12	− 4
R. W.	80	140/80	72	0.23	+ 6	+11	0.31	+22	−22	"	25	0.23	+14	−	+11	0.32	+12	45	− 5
F. R.	94	120/88	76	0.11	− 3	+40	0.16	+22	−16	"	30	0.11	+ 7	−	+14	0.16	+16	36	− 4
																0.32	−31		− 4
J. S.	91	108/70	84	0.05	− 8	+14	0.09	+24	−14	D.H.K.	0.5					0.09	+25	0	−14
				0.10	− 9	+19	0.26	+41	−24			0.10	−11	−	+18	0.26	+37	10	−23
				0.20	+ 9	+24						0.20	+10	−	+22				
E. W.	60	102/62	76	0.25	+41	+10	0.13	+20	−11	C.C.K.	0.3	0.25	+67	−	− 5	0.13	+23	0	−23
							0.40	+53	−31							0.40	+58	0	−40

* M.A.P. = "Mean" Arterial Pressure = $\frac{\text{Systolic} + \text{Diastolic}}{2}$

† % Inhibition = Control B.P. Change − $\frac{\text{After Drug B.P. Change}}{\text{Control B. P. Change}}$

mg. of benzodioxane was also administered during the infusion of a minimal pressor dose of norepinephrine (0.1 microgram per Kg. per minute) with a resulting 75 per cent inhibition of the hypertensive response. The duration of the inhibiting effect was only two minutes. It is of interest that one week previously the same patient had received Dibenamine in a dose of 6 mg. per Kg. (table 1). Following Dibenamine the norepinephrine pressor response was completely abolished even with infusion rates of norepinephrine which were four times greater than those used during the benzodioxane experiments.

Effect of the Imidazoline Derivatives, Priscoline and C-7337

Two subjects received 25 to 125 mg. of. Priscoline while 3 others received 25 to 50 mg. of C-7337. All doses were given intravenously. The effects of both drugs were essentially similar. In all cases epinephrine reversal occurred even at relatively high infusion rates (case S. P., table 1). The tachycardia that resulted from epinephrine infusion was exaggerated. However, in contrast to the results obtained with Dibenamine, the imidazoline compounds only partially inhibited (0 to 76 per cent; average 60 per cent inhibition) the pressor response to norepinephrine.

Effect of Tetraethylammonium (TEA) and Hexamethonium (C6)

Since both of these drugs inhibit transmission through autonomic ganglia they are considered together. It was more convenient to study the effects of ganglionic blocking agents using C6 since this drug has a longer duration of action than TEA.[7] Three subjects received 35 to 50 mg. of C6 intravenously. In all of these cases the pressor effects of both epinephrine and norepinephrine were intensified (table 1). The results were similar in 2 subjects who received 350 and 400 mg. respectively of TEA intravenously.

Effect of L-Hydrazinophthalazine

Three subjects were given L-hydrazinophthalazine (C-5968) in doses of 18 to 30 mg. (0.31 to 0.37 mg. per Kg. body weight) intravenously. A fall in arterial pressure occurred in one case and an increase in heart rate developed in 2 cases approximately 15 minutes after the drug was administered. Twenty minutes after C-5968 was given the responses to epinephrine and norepinephrine were tested.

No consistent effects were observed in regard to the epinephrine response. In one instance there was slight inhibition of the epinephrine pressor response and in 2 cases there was slight potentiation. The degree of tachycardia was uninfluenced in 2 cases and slightly inhibited in the other. The pressor response to norepinephrine, however, was moderately reduced in all instances (12 to 45 per cent inhibition). In addition, there was almost complete abolition of the bradycardia accompanying the norepinephrine induced hypertension. This marked inhibition of heart rate occurred despite elevation of mean arterial pressure as high as 30 to 45 per cent above the basal values.

Effect of the Dihydrogenated Alkaloids of Ergot

Previous studies[8] utilizing the same technics have demonstrated that the dihydrogenated alkaloids of ergot were very weak adrenolytic agents in the dosages customarily used in man. For the sake of completeness, however, and to test the effects of these drugs on the cardiovascular responses to norepinephrine, 2 patients were studied before and after the intravenous administration of the dihydrogenated alkaloids. One case was given 0.5 mg. of dihydroergokryptine while the other received 0.3 mg. of the combined dihydrogenated alkaloids (C. C. K.). In neither instance was significant inhibition of the cardiovascular responses to either epinephrine or norepinephrine observed.

Discussion

The effects of the various "sympatholytic" drugs on the pressor response to epinephrine appear to be similar in both man and animals. Thus, in animals, epinephrine reversal has been demonstrated after Dibenamine,[9] Priscoline,[10] C-7337[11] and benzodioxane. In addition, inhibition of epinephrine induced hypertension has been demonstrated in man after Dibenamine,[12] Priscoline[13] and benzodioxane.[14] However, it was apparent from this study that the

epinephrine reversal produced by therapeutic doses of Dibenamine, Priscoline and C-7337 was more complete and lasting than that produced by similar doses of benzodioxane. The fleeting adrenolytic effect of benzodioxane has been noted previously by Prunty and Swan.[15]

In contrast, the effects of these agents on the hypertension resulting from norepinephrine has not been extensively investigated. In the present study Dibenamine produced the most complete inhibition of norepinephrine hypertension while Priscoline and C-7337 produced only partial inhibition. Benzodioxane also produced partial blockade, but, as with epinephrine, its action was fleeting, lasting less than two minutes.

It seems remarkable that benzodioxane which has such fleeting and relatively weak adrenolytic effects should be so reliable in predicting the presence of pheochromocytoma.[14] The results of this investigation suggest that a small dose of 15 to 20 mg. of Priscoline or C-7337 might be as reliable or perhaps more reliable than benzodioxane since such small doses of the imidazolines seldom produce significant reduction of basal arterial pressure; yet they would be expected to have a hypotensive effect in the presence of an excess of circulating epinephrine.

As has been observed in animal experiments ganglionic blocking agents such as TEA and C6 exaggerated rather than suppressed the hypertensive effects of both epinephrine and norepinephrine. It appears[16, 17] that this intensified response is due to blockade of the cardiovascular "moderator" reflexes of the autonomic nervous system, especially those reflex arcs originating in the carotid sinus and aortic arch.

Although the number of cases studied was small, there seemed to be a consistent quantitative difference in the action of Dibenamine as compared with the imidazoline compounds, Priscoline and C-7337. Although all of these agents produced epinephrine reversal, there was more complete inhibition of the effects of norepinephrine following Dibenamine than following the imidazolines. These results apparently were not due to dosage differences since the degree of norepinephrine blockade was greater after minimal effective doses of Dibenamine than after relatively large doses of Priscoline and C-7337. These data suggest, therefore, that Dibenamine is an active blocking agent for both epinephrine and norepinephrine whereas the imidazoline compounds, while qualitatively similar, are potent blocking agents for epinephrine but are less active against norepinephrine. In this regard it may be of interest that in animals the dosages of Priscoline and C-7337 required to produce epinephrine reversal are far less than the amount required to block sympathetic nerve stimulation,[11] whereas with Dibenamine this difference in dosage is less.[1]

The action of L-hydrazinophthalazine (C-5968) differs from that of any of the other agents. In animals given larger doses than those used clinically in man the drug moderates but does not block epinephrine and norepinephrine hypertension nor does it produce epinephrine reversal.[18–20] In the present study there appeared to be slight inhibition of the norepinephrine but not the epinephrine pressor response. However, the most striking observation was the marked inhibition of the bradycardia induced by norepinephrine. The significance of this observation is not clear; since the bradycardia probably is reflex in nature, it may be that C-5968 interrupts the reflex arc at an unknown point.

The present study demonstrates the difficulty in classifying autonomic blocking agents according to a simple schema. The concept of central, ganglionic and peripheral blocking agents is a useful but crude approximation. Thus, Dibenamine, the imidazolines and L-hydrozinophthalazine all appear to exhibit distinctive differences in their ability to inhibit the cardiovascular effects of epinephrine and norepinephrine. This suggests that each of these drugs may act at different points in the chain of reactions involved in the activation of effector cells.

Summary

The effects of various "sympatholytic" drugs on the pressor responses to epinephrine and norepinephrine were investigated under controlled conditions in man. The dosages used approximated those customarily employed clinically.

1. Following Dibenamine there was "reversal" of the pressor response to epinephrine and complete or nearly complete abolition of the pressor response to norepinephrine.

2. The imidazolines (Priscoline and C-7337) also produced epinephrine reversal but only partially inhibited the hypertension induced by norepinephrine.

3. Benzodioxane irregularly produced epinephrine reversal and only partially inhibited the pressor response to norepinephrine. The adrenolytic effect was of fleeting duration.

4. L-hydrazinophthalazine failed to affect epinephrine responses, slightly inhibited the norepinephrine pressor response and almost completely blocked the bradycardia induced by norepinephrine.

5. Ganglionic blocking agents such as tetraethyl ammonium and hexamethonium intensified the pressor effects of both epinephrine and norepinephrine.

6. Clinical doses of the alkaloids of ergot had little or no inhibiting affect of epinephrine and norepinephrine pressor responses.

7. Although, in general, agents which inhibit or reverse epinephrine hypertension also modify the norepinephrine pressor response, there appear to be quantitative differences in the degree of inhibition obtained with different agents.

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Effects of Bleeding on Electrolyte Excretion and on Glomerular Filtration

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Removal of small amounts of blood from sitting subjects caused reduction of sodium excretion without alterations in creatinine clearance, or in apparent cardiac output (electrokymographic method). This reduction could be prevented by compression of the neck. The experiments support the concept of an homeostatic central mechanism which regulates the volume of extracellular fluid by altering sodium excretion. If such a mechanism exists it is apparently activated by changes in the volume of body fluids rather than by changes in cardiac output.

PREVIOUS studies[1-3] have shown that compression of the neck causes increased urinary excretion of sodium in the sitting position, but has little or no effect in the recumbent position. Marked decline in urinary sodium, which ordinarily occurs in the sitting as compared to the recumbent position, can be partially although not completely prevented by compression of the neck. The data were interpreted as indicating the probable existence of some central mechanism concerned in the regulation of electrolyte excretion, apparently set into operation by alterations in the volume of fluid in the cranial cavity or by some closely related factor. The present study is the first of a number aimed at further elucidating the nature of the mechanism.

Methods

General Plan of Experiments. Normal healthy young men were bled, and measurements of electrolyte excretion and glomerular filtration rate were made. The symptoms were observed, and blood pressure and pulse rate were measured before and after bleedings. Observations of the effect of bleeding on the apparent cardiac output (electrokymographic method) were also made.

In the beginning, there was some doubt as to how much blood needed to be removed in order to produce alterations in the excretion of sodium. Hence a series of preliminary experiments was done, and it was found that the amount of bleeding needed to produce changes varies markedly with posture (fig. 1).

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In order to determine whether loss of blood from the head was of any particular significance, further experiments were done in which the bleeding was repeated while the neck was compressed by a blood pressure cuff inflated to 20 mm. of Hg.

Experimental Procedure. In the case of the earlier experiments a standardized diet was not employed on the days prior to the experiment, but the amount of added sodium chloride ingested was kept constant at approximately 5 Gm. The later experiments were done on individuals previously receiving, over a period of several days, a standardized diet containing 1 Gm. of sodium, to which on each day 7.5 Gm. of sodium chloride were added in three approximately equal amounts, divided among the three meals.

The subject came to the laboratory on the day of the experiment and consumed no food other than either half of a chocolate bar each hour, or one egg every two hours, as preferred, the food being constant for different experiments on the same subject. A solution of 0.14 per cent sodium chloride was employed for loading in order to maintain urine volumes of convenient size, to prevent markedly negative sodium balance during the experiment, and to achieve the strictest constancy of hourly sodium output. The subjects drank 200 ml. of this solution at hourly (recumbent) or half-hourly (sitting) intervals. This difference in technic employed in the two positions was found, in a previous study,[3] to be desirable in order to minimize the progressive rise in the excretion of water and sodium which tended to occur during the first several hours after the onset of loading.

Urine was voided and collected at hourly intervals for a period of 10 hours. Since the excretion of water and of sodium usually increased rapidly during the first two hours, the data reported are only those for the third or fourth and subsequent hours. Cigarette smoking was permitted hourly in some subjects and as desired in others.

In some instances (the control experiments) the

procedure was constant throughout for a period of 10 hours, while in other instances the subject was bled at the end of the fourth hour of loading. The procedure was then continued for a second four hour period, after which the blood plus 80 ml. of 3.3 per cent sodium citrate was reinfused, the ingestion of the solution and the collection of urine being continued for two subsequent hours. In a third series of observations the identical procedure was followed except that a blood pressure cuff around the neck was inflated to 20 mm. of Hg, and kept in place from the time bleeding was started until the reinfusion was completed.

The experimental procedure as described was that followed for the experiments carried out in the sitting posture. The procedure utilized in the recumbent subjects differed in certain respects. The preparatory diet was not utilized for the several days before the experiment. Although the same loading solution was used, only one-half as much (i.e., only 200 ml. per hour) was ingested. A control experiment without bleeding was omitted and a larger amount of blood (9 ml. as compared to 2.5 ml. per Kg. of body weight) was removed. Observations in the recumbent posture were made on bleeding in the horizontal position with and without compression of the neck and on bleeding in the head-down (Trendelenburg) position, the angle of the bed being approximately 20 degrees from the horizontal.

The technics utilized for sodium, potassium, chloride, glomerular filtration, and for the apparent cardiac output (as calculated from electrokymographic tracings), were identical with those employed in the previous study.[3] It is realized that the electrokymographic method for cardiac output may not yield correct absolute values, but there is evidence[4,5] that the procedure provides an accurate qualitative index of directional changes.

Results

The Amount of Bleeding Necessary to Affect Sodium Excretion. In the control experiments the subjects were not bled but continued to ingest the loading solution. Under these conditions it was clear that an equilibrium state was not obtained in the earlier hours of loading, as the sodium excretion was greater in the later than in the earlier hours.[3] This occurred in both postures. Bleeding (2.5 ml. and 9.0 ml. per Kg. in the sitting and recumbent postures, respectively) did not always cause an absolute decline in urinary sodium, but did cause either an absolute decline or an inhibition of the rise which occurred during the later hours in the control experiments (fig. 1). Because of the greater tendency toward syncope in the sitting posture, larger amounts of blood were not removed in this position. In the recumbent posture the removal of larger amounts (9 ml. per Kg.) caused a striking decline in sodium output. These preliminary experiments indicated clearly that sodium excretion is much more readily depressed by bleeding in the sitting than in the recumbent position. In subsequent experiments the amounts of blood removed were, therefore, 2.5 ml. per Kg. in the sitting subjects (in order to study the mechanisms concerned in the more delicate regulation of sodium excretion) and 9 ml. per Kg. in the recumbent position (in order to investigate any possible additional mechanisms). The results obtained in the two positions may now be considered.

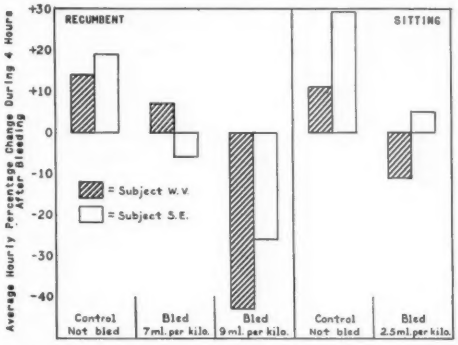

FIG. 1. Mean change in urinary sodium excretion produced by bleeding in two subjects in recumbent and sitting postures. The results of preliminary experiments designed to determine the amount of bleeding necessary to affect sodium excretion are depicted. In both postures a gradual rise in sodium excretion occurred during the control periods without bleeding. Removal of 2.5 ml. of blood per Kg. in the sitting position had about the same effect as removal of 7.0 ml. per Kg. in the recumbent position. Both procedures caused little absolute change in sodium output but inhibited the rise which occurred during the same hours in the control experiments. Bleeding larger amounts—9 ml. per Kg.—in recumbent subjects caused a well marked absolute decline in urinary sodium. Because of the tendency toward syncope in the sitting position larger amounts were not removed in this posture.

Studies in the Sitting Position

Although these studies were actually done last, they will be considered first because they

seemed to yield the more significant results. The subjects experienced minimal or no symptoms except that following the reinfusion of blood slight discomfort, consisting of slight

four experiments is portrayed in figure 2. During the control periods without bleeding a minimal decline tended to occur, and no greater decline occurred as the result of the bleeding.

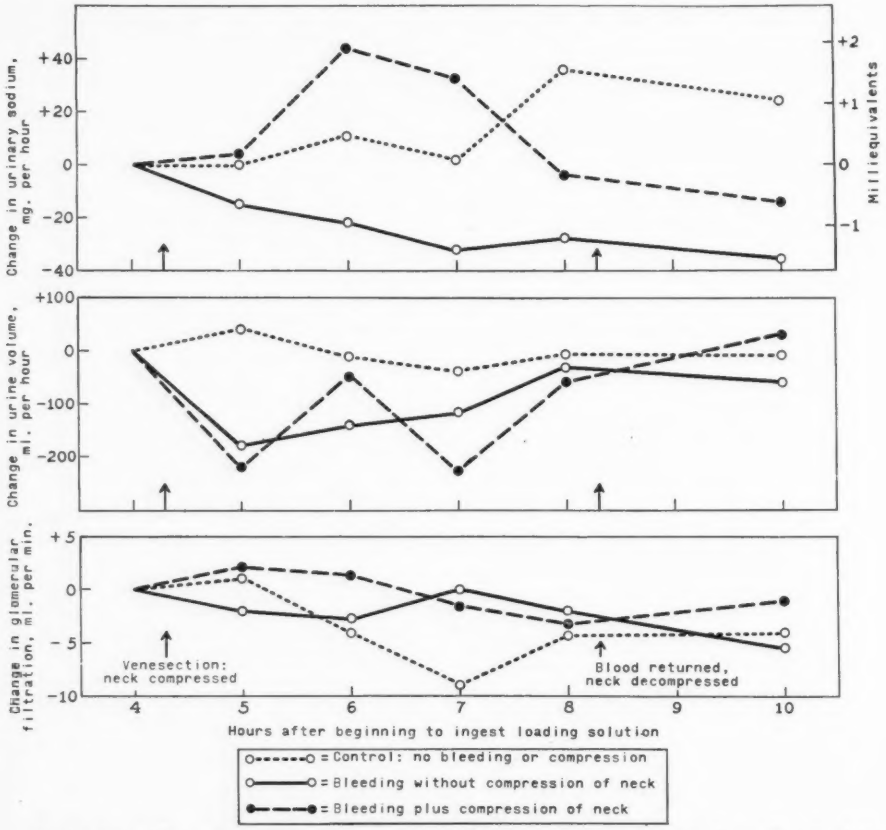

FIG. 2. Mean alterations produced in 4 normal subjects by venesection, 2.5 ml. per Kg., in sitting position. The data for the first three hours are omitted because excretion of water and sodium varied widely during this preliminary period of loading. The data for the ninth hour, during which the removed blood was reinfused, are also omitted because mild symptoms of alkalosis due to infusion of citrate often occurred at this time.

Significant changes in glomerular filtration were not encountered. Bleeding caused a sharp reduction in urine volume, the effect not being significantly altered by compression of the neck.

In the control experiments a gradual rise in sodium excretion occurred. Bleeding caused a decline in sodium excretion but bleeding while the neck was compressed was followed by a rise in sodium output.

numbness and tingling, occurred at times. These manifestations were thought to be due to the sodium citrate solution.

Consistent alterations in pulse rate and blood pressure were not observed as result of the bleeding.

Glomerular Filtration. The average result in

Comparison of the results during the four hours following bleeding with those of the hour immediately preceding and with those of the second hour following reinfusion revealed no significant alteration as the result of compression of the neck.

Urine Volume. During the first two or three

hours of loading a progressive increase in urine volume occurred. The data obtained during these hours in which equilibrium was being obtained are not shown in the tables or figures. During subsequent hours relatively slight fluctuations in the average urine volume occurred during the control experiments in which bleeding was not done (fig. 2). In those observations in which the subject was bled, either with or without compression of the neck, an immediate decline in urine volume occurred during the first posthemorrhagic hour, bled, the urinary sodium underwent an absolute decline in 3 of the 4 subjects and a relative decline (i.e., a less striking rise than in the control experiment without bleeding) in the fourth individual. The average effect of bleeding was a reduction in sodium excretion which was small in actual value when compared with the sodium excretion immediately before the bleeding, but was of considerable magnitude when compared with the tendency to rise in the control experiments in which bleeding was not done. Reinfusion of such small amounts of

TABLE 1.—*Effect of Bleeding and Reinfusion, with and without Compression of the Neck, on the Urinary Sodium Excretion of Subjects in the Sitting Position.*

Procedure	Subject	Sodium Excretion per Hour: Mg.					
		Before Procedure*	During Procedure				After Procedure†
			1st hour	2nd hour	3rd hour	4th hour	
Control: no bleeding or compression	B. O.	198	165	159	157	166	168
	T. L.	154	150	138	123	174	135
	S. E.	161	191	243	237	261	259
	W. V.	206	216	226	214	270	255
Venesection: 2.5 ml. per Kg. Reinfusion after four hours.	B. O.	251	159	216	231	179	135
	T. L.	161	171	99	99	127	—
	S. E.	201	202	236	213	198	192
	W. V.	167	193	143	111	167	152
Venesection: 2.5 ml. per Kg. plus compression of neck. Reinfusion and decompression after four hours.	B. O.	168	213	314	305	231	213
	T. L.	388	436	369	302	220	212
	S. E.	249	203	278	266	259	272
	W. V.	190	156	220	252	265	245

* The hour before procedure: the fourth hour of ingesting loading solution.

† The second hour after reinfusion. Results during first reinfusion hour omitted because of transient symptoms of alkalosis.

followed by a return toward the previous value. No striking difference was observed between the effects of bleeding when the neck was compressed and those in which bleeding alone was carried out. Reinfusion of the removed blood was without significant effect.

Sodium Excretion. The average findings for all of the subjects are presented in figure 2, and the observations on individual subjects are depicted in table 1. Rather striking findings were encountered.

In the control experiments without bleeding the excretion of sodium tended to decline or fluctuate in 2 of the subjects and to rise sharply in the other 2 individuals, the mean effect being a moderate rise.

On the contrary, when the subjects were blood (about 200 ml.) did not cause the sodium excretion to return to the previous level.

When the subject was bled while the neck was compressed, the decline in sodium was inhibited or prevented and the excretion of sodium somewhat greater than in the control experiments. Subsequently, the sodium excretion declined, but remained greater than that in the experiments in which bleeding was not accompanied by compression of the neck.

Chloride. Since, as will be indicated later, the excretion of this ion tended to parallel the excretion of sodium in other observations, measurements of chloride excretion were not made during this particular group of experiments.

Potassium. In most of the experiments,

regardless of the procedure employed, there was a general tendency for potassium excretion to decline as the experiment progressed. Since the loading solution was free of potassium and the subjects were, therefore, in negative potassium balance throughout, this trend would be expected, and probably reflects a tendency of the body toward conservation of this element. The experiments throw no light on the mechanism whereby such conservation was effected.

Comparison of potassium excretion under the various experimental conditions revealed no striking changes (fig. 3). It is evident either that bleeding and cervical compression had no significant effect, or that any action of these procedures on potassium excretion was masked by the general tendency toward decline during successive hours.

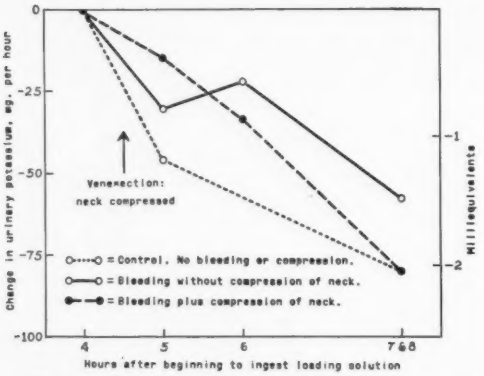

FIG. 3. Mean alterations produced in 4 normal subjects by venesection, 2.5 ml per Kg., in sitting position. The data for the first three hours and for the two hours following reinfusion are omitted for reasons given in the legend for figure 2. Potassium determinations were done on aliquots of the samples for the third and fourth hours following bleeding.

Neither bleeding 2.5 cc. per Kg. in the sitting position nor bleeding plus compression of the neck materially altered the progressive decline in potassium excretion which occurred in the control experiments.

Cardiac Output. It was not feasible to study this function during the same experiments in which the others were studied. Consequently, a separate group of experiments was carried out at a later date on the same subjects, who were bled the same amount under the same conditions. The data are presented in table 2. Significant changes in cardiac output were not observed as the result of the removal of such small amounts of blood (2.5 ml. per Kg. of body weight).

Studies in the Recumbent Position

Since the results, other than those for potassium excretion, were essentially similar for all four subjects, they are presented as averages in figure 4. Observations on individual subjects are depicted in table 3.

The clinical manifestations induced by removal of 9 ml. of blood per Kg. of body weight from recumbent subjects were variable and usually slight. Faintness, anorexia, and minimal headache were observed in several of the experiments. Compression of the neck did not seem to have any striking effect on the subjective response to bleeding. In the head-down position the same degree of bleeding caused fewer symptoms than in the case of the horizontal subjects. On several occasions when the subjects were bled in the horizontal recumbent position and developed symptoms, it was found that prompt relief occurred with elevation of the foot of the bed.

Glomerular Filtration. The average findings are presented in figure 4. Both in the horizontal and head-down positions, bleeding without compression of the neck was followed by a slight but definite decline during the next one or two hours, with a return to the prebleeding level during subsequent hours, no significant alteration being induced by reinfusion of the subject's blood. The alterations in glomerular filtration, when the bleeding was done while the neck was compressed, were somewhat greater (fig. 4) than in the case of the experiments in which the neck was not compressed, but the difference was slight and of doubtful significance.

Urine Volume. This function declined sharply during the first two hours after bleeding, and then increased slowly, reinfusion being followed by a rise to or above the control level. The responses were essentially similar in the head-down and in the horizontal positions with and without compression of the neck.

Sodium Excretion. This function declined

slightly during the first hour, more during the second, and most strikingly during the third and fourth hours, after the bleeding (fig. 4). A definite rise was noted following the reinfusion of removed blood. Compression of the neck had no definite effect on the alterations of sodium excretion produced by bleeding when the subject was in the recumbent position. The average decline with the head down was somewhat less than when horizontal, but the difference was not impressive and is of doubtful significance.

Chloride. The changes paralleled the changes in sodium, a definite decline being induced by bleeding but a less marked rise occurring after reinfusion (table 3). (The difference between chloride and sodium in this respect, which was consistent, may possibly have been dependent on the use of sodium citrate as an anticoagulant.) There was no obvious difference between the experiments in which the neck was compressed and those in which this procedure was omitted. Chloride excretion was not measured in those experiments carried out in the head-down position.

Potassium. Since the different subjects who displayed similar results in regard to the other functions studied exhibited rather striking variations as regards potassium excretion, the data are summarized for each individual (table 3) and are compared with sodium, chloride, filtration rate, and clinical manifestations.

In some instances venesection had no apparent effect on potassium excretion which declined progressively as in control experiments. In other instances a temporary rise in potassium excretion occurred following venesection.

Since only a few control studies were made in which the entire procedure other than venesection was carried out, the interpretation of these results is uncertain. Possibly the initial rise in urinary potassium after bleeding was not caused by bleeding but was related to a lag in the effect of loading and comparable to that often observed during the first two or three hours. If so, this lag occurred later than usual because the lag was ordinarily not noticed as late as the fifth hour of loading. Another possible explanation is that in those subjects who exhibited the initial posthemorrhagic rise in potassium excretion, the venesection caused increased activity of the adrenal cortex. In favor of this interpretation is the observation that the increase was associated with a decline in sodium excretion. Against this interpretation is the rapid onset and the short duration of the rise in potassium excretion.

Potassium determinations were not done in the head-down experiments.

Cardiac Output. The data are shown in table 2. One subject exhibited no significant change in this function; another displayed an apparent rise. Since the control value was unusually low for the subject while the values obtained after bleeding were within the range of the control values usually encountered in the same

TABLE 2.—*Effects of Bleeding* on Diameter, Excursion and Apparent Output of the Heart (Electrokymographic Method).*

Subject and Position	Diastolic Thickness: cm.				Systolic Excursion: cu..				Apparent Stroke Volume: ml.				Apparent Cardiac Output per min.: liters			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
W. V. (Sitting)	7.50	7.34	7.34	7.34	.51	.53	.53	.50	90	91	91	86	7.1	7.2	6.9	7.1
T. L. (Sitting)	6.79	6.44	6.52	6.44	.60	.51	.48	.54	95	77	74	81	6.6	6.1	6.1	6.1
B. O. (Sitting)	6.12	6.76	6.82	6.67	.44	.44	.47	.43	63	69	77	69	4.6	4.6	5.3	4.3
S. E. (Sitting)	7.20	7.24	6.89	6.71	.51	.52	.52	.57	86	89	84	89	6.5	6.6	6.4	6.7
S. E. (Recumbent)	6.74	6.73	6.95	7.25	.52	.56	.58	.55	82	88	94	93	5.0	6.9	6.6	6.8
W. V. (Recumbent)	7.03	7.32	7.04	6.92	.79	.70	.73	.72	128	119	119	115	7.1	7.5	7.5	7.3

A = Control, before bleeding
B = 15 minutes after bleeding
C = 45–60 minutes after bleeding
D = 2 hours after bleeding

* Subjects bled: 2.5 ml. per Kg. in sitting position; 9 ml. per Kg. in recumbent position.

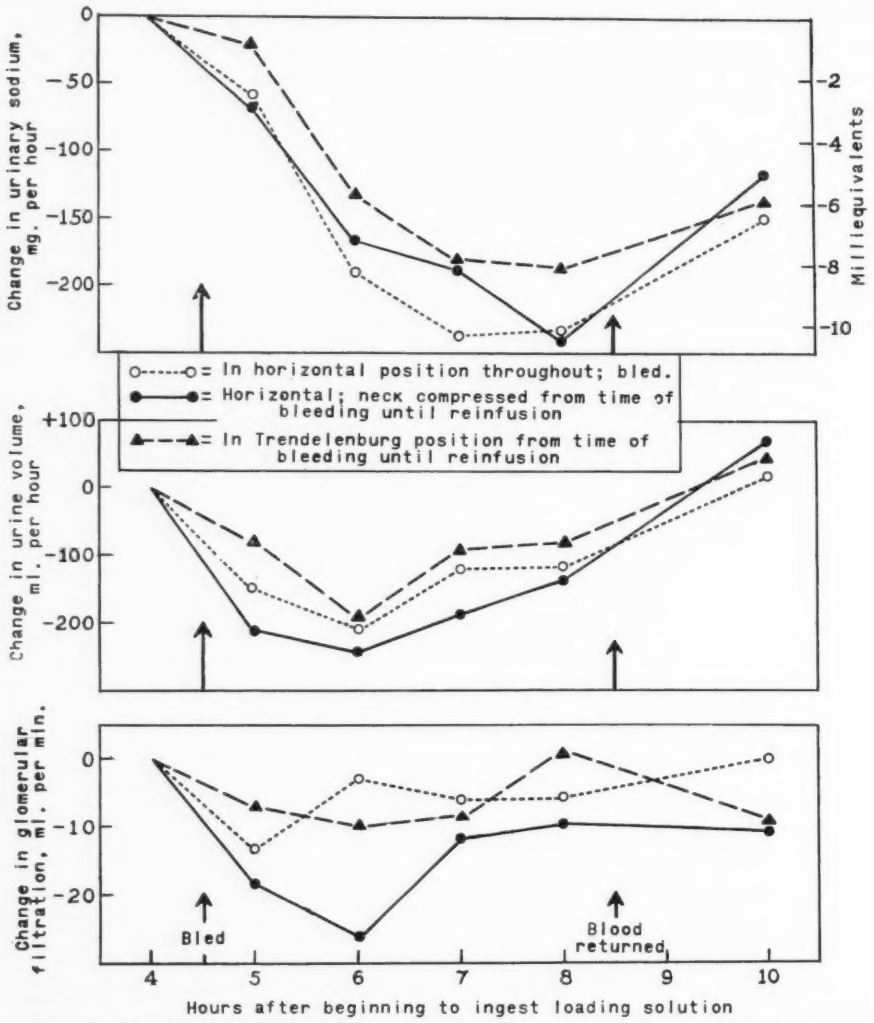

FIG. 4. Mean alterations produced in 4 normal subjects by venesection, 9 cc. per Kg., in recumbent position. In recumbent subjects minimal decline in glomerular filtration and well marked decline in urine volume occurred following bleeding.

The decline in sodium excretion following venesection in the recumbent position was not significantly altered by compression of the neck or lowering the head. This decline tended to be maximal three to four hours after venesection in contrast to the declines in urine volume and glomerular filtration which were maximal in the first or second hour.

individual, it seems unlikely that the increase observed after bleeding is of any significance. The data confirm those of other investigators in indicating that removal of relatively large amounts of blood in recumbent normal subjects has no constant effect on cardiac output.[6]

The Differences between the Effects of Bleeding in the Various Postures.

Comparisons in which identical amounts of blood were removed are not available because the preliminary experiments (fig. 1) indicated clearly that sitting subjects were much more

sensitive to removal of a given amount of blood than were recumbent subjects. As well as could be judged from the few studies made, the removal of about 3 ml. per Kg. in the sitting position can be expected to cause about the same reaction (minimal faintness and/or slight headache) as the removal of 7 or more ml. in the horizontal position. It was clear that the head-down position was the most favorable for the prevention of symptoms, as none of the subjects experienced significant subjective response to the removal of 9 ml. of blood in this posture, while the reactions occasionally produced by removing the corresponding amounts from horizontal subjects were promptly ameliorated by elevation of the foot of the bed.

The data indicate that the amount of blood which must be removed in order to produce a decline in sodium excretion is considerably greater in the recumbent than in the sitting subject (fig. 1). They also indicate that in the sitting posture the effects of bleeding on sodium

TABLE 3.—*Alterations Produced in Four Normal Subjects by Venesection, with and without Compression of the Neck, in the Recumbent Position.*

Hour†	Subject B. O.				Subject T. L.				Subject S. F.				Subject W. V.			
	Sodium mg./hr.	Chloride mg./hr.	Potassium mg./hr.	Filt. Rate ml./min.	Sodium mg./hr.	Chloride mg./hr.	Potassium mg./hr.	Filt. Rate ml./min.	Sodium mg./hr.	Chloride mg./hr.	Potassium mg./hr.	Filt. Rate ml./min.	Sodium mg./hr.	Chloride mg./hr.	Potassium mg./hr.	Filt. Rate ml./min.
	Recumbent Bleeding Experiment															
−1	370	524	91	104	520	910	178	106	215	416	131	109	438	707	205	127
	9 ml. Blood per Kg. of Body Weight Withdrawn															
	Syncopal Symptoms								Syncopal Symptoms							
+1	213	346	128	90	535	912	117	108	200	450	137	73	406	622	163	123
+2	136	193	56	103	243	844	72	109	148	304	95	100	287	476	122	126
+3	150	220	61	105	166	866	52	105	159	311	98	98	213	728	83	123
+4	194	259	61	106	164	671	52	110	135	258	98	96	183	305	83	120
	Blood Returned															
Second hour after blood returned	276	225	*	103	294	412	*	109	183	241	*	110	213	247	*	131
	Recumbent Bleeding plus Compression of the Neck															
−1	456	668	235	132	178	233	56	104	326	526	172	114	402	595	139	131
	9 ml. Blood per Kg. Removed and Neck Compressed															
+1	360	566	247	114	73	119	92	86	302	470	196	108	367	582	138	105
+2	193	396	122	132	38	66	48	40	211	385	167	106	243	399	110	106
+3	224	399	91	123	30	116	43	107	189	316	96	107	191	337	86	108
+4	211	324	91	121	434	217	43	110	158	256	96	110	174	293	86	114
	Blood Returned															
Second hour after blood returned	272	451	*	120	262	284	*	106	177	259	*	109	249	284	*	113

* (1) Determinations of potassium excretion following reinfusion of blood not done because the alkaline anticoagulant citrate solution should completely disturb potassium metabolism equilibrium.
(2) Average hourly potassium determinations done on urine samples at hours 3 and 4 after bleeding.
† The number of the hour before and after removal of blood.

excretion may be overcome by compression of the neck and hence, presumably, by maintaining the intracranial fluid volumes. On the other hand, the decline in sodium output, which in the recumbent subject only occurs after removal of much larger amounts of blood, can be influenced little or none by measures, such as compression of the neck or institution of the head-down position, which would be expected to increase intracranial blood volume. These findings are in accord with those previously reported[3] in which it was shown that, in the absence of bleeding, compression of the neck, while causing a striking increase in the sodium excretion of sitting subjects, had little or no effect in recumbent individuals. The logical interpretation seems to be the assumption of multiple mechanisms controlling sodium conservation after bleeding, some of which are more readily activated in the sitting posture, others of which are more sensitive in the recumbent position. Such an assumption is not as paradoxic as might first appear if one visualizes the blood vessels as resembling readily collapsible rubber tubes. Withdrawal of a given amount of liquid from a vertically suspended tube would obviously cause greater decline in the volume of the "cephalic" end than would the same procedure with the tube in the horizontal position.

The Rates of Change of Various Functions Following Venesection

The data in figure 2 indicate a lack of relationship between glomerular filtration and sodium excretion following a small venesection in sitting subjects. Inspection of the data in figure 4 shows that following a large venesection in the recumbent subject, there was a general tendency for the declines in glomerular filtration and in urine volume to set in rapidly, and to become maximal during the first and second hours. On the other hand, the decline in sodium excretion was slight during the first hour and did not reach its peak until the third and fourth hours after venesection. Return of the removed blood caused the urine volume to return rapidly (within two hours) to somewhat above the initial level, while the sodium excretion rose slowly and still remained at a markedly depressed level during the second hour after transfusion.

These discrepancies between glomerular filtration and urinary sodium appear to justify two conclusions: (1) The decline in filtration, which was of lesser degree and of shorter duration, could not have been responsible for the decline in sodium output. (2) Apparently, different mechanisms were concerned in producing the changes in these functions. Renal vasomotor changes were probably concerned in the slight (but consistent) decline in glomerular filtration which occurred following the massive venesection. The alternative explanation of decline in cardiac output would seem to be excluded by the lack of reduction in this function (table 2).

The tendency of the decline in urine volume to occur somewhat later than the decline in filtration (fig. 4) is probably to be ascribed to the time required for the action of the antidiuretic hormone of the posterior pituitary to become manifest. The studies of Verney[7] and of Brun[8] would seem to make it likely that the oliguria following venesection, like that induced by orthostasis, emotion and exercise, is to be ascribed to the action of this hormone, but the mechanism of the stimulus remains obscure.

The data suggest that the changes in sodium excretion induced by bleeding are independent of alterations in glomerular filtration and in urine volume. The slower onset suggests a chemical rather than a neural mechanism. The decline induced by removal of small amounts of blood from sitting subjects could be inhibited by compression of the neck, and hence was presumably related to the mechanism previously described,[3] whereby alterations in intracranial fluid volumes (or some closely related factor) induce changes in urinary sodium. No such ready explanation is apparent for the decline in sodium excretion induced by the removal of large volumes of blood in the recumbent subjects. The failure of cervical compression or of the head-down position to overcome this effect would suggest that some other mechanism is concerned.

One might postulate that the removal of such large amounts of blood caused an alarm reaction, which brought the adrenal cortex into play. This possibility is considered later.

Mechanisms of Control of Sodium Excretion

The concept that alterations of glomerular filtration are of major importance in the more delicate regulation of sodium excretion is not supported by the findings. Likewise, the concept that decline in cardiac output initiates homeostatic mechanisms which result in tubular conservation of sodium finds no support in these data. It is reasonable to assume that decline in sodium excretion following hemorrhage constitutes an important mechanism of homeostasis, but the data indicate either that such mechanisms may be set into play by alterations in cardiac output of a degree too small to be detected by the methods used, or that some stimulus other than cardiac output is responsible.

Throughout these and other experiments various findings have emphasized the importance of the state of the sodium stores of the body as a factor of major significance in regulating the excretion of sodium. Thus in a parallel study,[3] it was found that observations on successive days in the recumbent posture were attended by a markedly negative sodium balance on the first day, and by a progressive decline in sodium excretion on successive days. In the sitting position under appropriate conditions the reverse situation obtained, the sodium balance being initially positive but the excretion rising subsequently until equilibrium between intake and output was achieved. The status of the subject, as regards sodium intake and sodium excretion during the period of several days prior to the experiment, has appeared to be the single most important factor controlling the absolute level of sodium output. This conclusion is similar to that arrived at by Couter and Leaf,[9] on the basis of prolonged studies of sodium balance.

The data obtained in the sitting subjects—decline in sodium excretion produced by venesection and prevented by compression of the neck—are compatible with the hypothesis, offered in previous publications,[1-3] that changes in the volume of blood or of extravascular fluid in the cranial cavity may be one factor concerned in the regulation of sodium excretion. The fact that injections of hypertonic albumin solution[10] and removal of blood both cause decline in sodium excretion would suggest that it may be the intracranial volume of extravascular fluid rather than of blood which is of importance in this respect. The possibility that the observed results may represent not a specific effect but rather the algebraic summation of two opposite effects, one of which (bleeding) tends to decrease and the other (compression of the neck) tends to increase sodium excretion, is not excluded by the data.

The effects of bleeding in the recumbent position do not support the assumption of the postulated intracranial mechanism. Here, compression of the neck did not prevent the decline in sodium excretion. The difference between these findings and those in the sitting position may perhaps be explained by assuming that in the sitting position the cranial cavity tends normally to be somewhat depleted of fluid, and that this depletion is aggravated by bleeding which, in the absence of suitable compensatory factors, would be expected to cause disproportionate depletion of the most elevated parts. In the recumbent position the cranial cavity would perhaps have more fluid initially, and removal of blood (even in larger amounts) might produce little or no deficiency of intracranial fluid because the gravity differential would no longer be operative. The analogy with the removal of fluid from a vertical versus a horizontal collapsible rubber tube has already been cited as offering a possible explanation for the apparently paradoxic results.

The foregoing considerations, while offering a possible explanation for the difference between the effects of cervical compression in the sitting and recumbent postures, do not offer an explanation for the decline in sodium excretion produced by bleeding in the recumbent subjects. In this respect, the increments of potassium excretion occurring in certain subjects (table 3) are of interest. Although the combination of a decline in urinary sodium plus a rise in urinary potassium suggests adrenal cortical activity, the rapid onset and short duration of the effect is not in keeping with the known actions of the cortical hormones. In any case, this explanation is not applicable to the decline in sodium excretion which occurred following recumbent bleeding in those subjects who exhibited no rise in

potassium excretion. It would appear that the mechanism responsible for the decline in sodium excretion following bleeding in the recumbent position is uncertain at the present time.

Summary and Conclusions

1. Removal of small amounts of blood (2.5 ml. per Kg. of body weight) from sitting subjects caused moderate decline in the excretion of sodium without demonstrable alterations in cardiac output or in glomerular filtration. The reduction in sodium excretion could be prevented by compression of the neck. The findings suggest that the decline in sodium excretion produced by bleeding under these conditions may have been related to alterations in the distribution of blood and/or extravascular fluid and, more particularly, to reduction of the fluid volumes in the cranial cavity.

2. Removal of larger amounts of blood (9 ml. per Kg. of body weight) from recumbent subjects caused a striking decline in the excretion of sodium. This could not be prevented either by compression of the neck or by elevation of the foot of the bed, although the latter procedure tended to alleviate the syncopal symptoms often induced by the bleeding. Slight reduction in glomerular filtration usually occurred but was of brief duration, and the maximum decline in sodium output occurred after the filtration rate (creatinine clearance) had returned to the normal level. Consistent alterations in cardiac output (as measured by the electrokymographic method) were not encountered. Possible mechanisms of the decline in sodium excretion are discussed.

3. The excretion of chloride tended to parallel that of sodium. Venesection appeared to cause rise in potassium excretion in some experiments but not in others.

4. The experiments support the concept of a homeostatic mechanism concerned with sodium conservation. They suggest that such a mechanism may be initiated by multiple processes, of which one appears to be alterations in the distribution of blood within the body. The experiments do not support the idea that decline in cardiac output constitutes a stimulus to retention of sodium and chloride.

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Adhesiveness of Blood Platelets in Arteriosclerosis Obliterans, Thromboangiitis Obliterans, Acute Thrombophlebitis, Chronic Venous Insufficiency and Arteriosclerotic Heart Disease

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Total and adhesive platelet counts were made on normal individuals and on patients with myocardial infarction, thromboangiitis obliterans, and other peripheral vascular diseases. Tests were made in several cases while patients smoked and after abstaining from tobacco. Repeated tests were done while patients were receiving dicumarol anticoagulant therapy. A rise in adhesive platelet counts was found in cases of thromboangiitis obliterans, particularly with activity of the disease, and in cases of thrombophlebitis. Cessation of cigarette smoking in cases of thromboangiitis obliterans resulted in a significant decrease in platelet adhesiveness.

THE PURPOSE of this paper is to present statistical evidence of the clinical significance of the glass wool filter test of adhesiveness of blood platelets described by Moolten and associates,[3, 4, 5] in 125 cases of peripheral vascular and arteriosclerotic heart disease. At first this test was utilized in patients with existing or impending coronary thrombosis in an attempt to correlate it with the clinical and electrocardiographic findings. We were unable, however, to duplicate the results of Moolten and Vroman in this field or to find any correlation. The glass wool filter test was then applied to cases of various types of peripheral vascular disease and striking differences were found. We are indebted to Sylvan Moolten for instruction in the exacting technic of this test.

Method

The method described by Moolten and co-workers was used. This method was chosen rather than that of Helen P. Wright[2] because of its greater simplicity and speed. A specimen of citrated venous blood was filtered through a fiber glass wick. Pre- and postfiltration red cell and platelet counts were performed. From this data the number of adhesive platelets was calculated, using a simple formula devised by Moolten.

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Factors Effecting Adhesiveness

It has been demonstrated by Wright, Moolten and others[1–5] that the following factors increase the adhesiveness of platelets: accidental and surgical trauma, the postpartum state, carcinoma and hemorrhage. Conversely, the following conditions decrease platelet adhesiveness in vivo and in vitro: increased concentrations of citrate, oxalate, heparin and dicumarol.

Origin of Platelets and Function

Platelets are derived from megakaryocytes in the bone marrow and constitute the basic foundation of a white thrombus, which is the initial stage of intravascular clotting. It is believed by Wright[2] that fibrinogen is converted into fibrin on the surface of the platelets and that adhesiveness is the result of this change. It seems reasonable to assume that increased adhesiveness of platelets suggests the presence or imminence of thrombosis. A secondary function of platelets in the white thrombus may be liberation of a vasoconstrictor substance.

Factors Affecting the Adhesive Platelet Count

Anticoagulant therapy in the form of dicumarol was found to produce a marked decrease in the adhesive platelet count in active thromboangiitis obliterans associated with or without superficial migratory phlebitis and a subsidence of clinical manifestations. When dicumarol was discontinued, the adhesive platelet count became elevated.

In active thromboangiitis obliterans the adhesive count was markedly increased whereas in inactive thromboangiitis obliterans the count was elevated above the normal range but was not as high as in the active cases.

Of our control series of 100 normal subjects, it was found that approximately 70 per cent were smokers. Adhesive platelet tests performed on this group of smokers were in the same range as those found in normal nonsmokers. About 35 per cent of this group of normal smokers completely refrained from smoking for periods of one to two weeks and tests made at the end of this period revealed no change from the previous adhesive platelet counts. Serial tests were performed in the clinic and in private practice on many of the arteriosclerotic peripheral vascular patients who smoked and revealed no change from the normal count. Twenty-five of the arteriosclerotic patients who smoked refrained from smoking for periods of one week and tests taken at the end of this time revealed no change in their adhesive counts.

In the thromboangiitis obliterans series most of the patients claimed to have stopped smoking, but in this group the adhesive count was elevated whether the patient smoked or not. In the case of W. K. there was a history of myocardial infarction which preceded the onset of thromboangiitis obliterans by one year. This patient was a heavy smoker at the time of his coronary thrombosis. He recovered but continued to smoke heavily. A test done while smoking revealed an exceptionally high adhesive platelet count. When he refrained from smoking for only three days there was a sharp decrease of 50,000 adhesive platelets.

In a few other cases of thromboangiitis obliterans with ulceration, serial tests revealed a decrease in adhesiveness on cessation of smoking with a coincidental improvement in ulcers. When smoking was resumed, the platelet adhesiveness was increased.

The group of patients with arteriosclerotic peripheral vascular disease associated with arteriosclerotic heart disease showed no change from the normal range of platelet adhesiveness. An adhesive platelet test was done on a private male patient aged 62 years, suffering from arteriosclerotic heart and peripheral vascular disease, and revealed a normal count. Two days later he complained of acute substernal distress of a few hours duration. A count was done immediately but no significant change was found. The first count was 65,000 and the second, 67,000. The next day the patient died of acute coronary thrombosis.

In our series of one case with acute deep thrombophlebitis and 6 cases of chronic venous stasis resulting from deep thrombophlebitis, adhesive platelet counts were all significantly elevated. In lymphedema, although the lower extremity is also swollen, the adhesive count falls within the normal range.

In an acute flare-up of thromboangiitis obliterans or deep thrombophlebitis in the form of superficial migratory phlebitis, there was found to be a marked elevation in the adhesive platelet count.

Serial tests were done on 5 cases of lupus erythematosus disseminatus before and during cortisone therapy to determine if the dramatic response to this therapy was due in any part to its effect on platelet adhesiveness. There was no change in total or adhesive platelet counts during cortisone therapy.

Results

We felt that in order to derive any clinical significance from the adhesive platelet counts in specific pathologic conditions, it was essential to have a large series of normal adhesive counts from which to determine the mean normal adhesive count and the standard deviation. Over 100 normal individuals ranging in age from 20 to 45 years were tested and approximately 200 tests were performed on these normal subjects. It was found that the normal mean was 67,000 adhesive platelets with a

standard deviation of 18,000. Our normal figures were appreciably lower than those found by Moolten[3–5] (fig. 1).

In a series of 36 cases of thromboangiitis obliterans in which seventy tests were performed, there was found to be an increase in adhesiveness of platelets, with a mean count of 111,500 and a standard deviation of 40,000. This series was subdivided into the following groups: those with ulceration, diabetes, coronary thrombosis, combined arteriosclerotic peripheral vascular disease and thromboangiitis obliterans, uncomplicated (fig. 1).

While the majority of all these groups showed a markedly elevated adhesive platelet count, this was most striking in a young patient with a combination of thromboangiitis obliterans and arteriosclerotic heart disease. He was also a very heavy cigarette smoker. This particular case was in marked contrast to our series of 12 cases of acute myocardial infarction in which fifty-five tests were done; these did not reveal any significant increase in platelet adhesiveness. Tests were performed daily on these cases and we were unable to determine any essential difference from those of our series of 100 normal cases.

In a series of 60 cases of arteriosclerotic peripheral vascular disease in which approximately seventy-five tests were performed, the mean adhesive platelet count was 75,000 with a standard deviation of 19,000 (fig. 1). This series was also subdivided into five groups similar to those applied to cases of thromboangiitis obliterans.

In a group of 7 cases, one of acute deep thrombophlebitis and 6 of residual venous stasis resulting from thrombophlebitis, the mean adhesive platelet count was 166,000 (fig. 1).

From the above data it is apparent that the patients with arteriosclerotic peripheral vascular disease have an adhesive platelet count only slightly above the normal range, whereas those with thromboangiitis obliterans and deep thrombophlebitis have a marked elevation of adhesiveness. It is of interest to note that the presence of gross ulceration complicating arteriosclerotic disease caused no appreciable increase in platelet adhesiveness, while in thromboangiitis obliterans there was a very significant increase in platelet adhesiveness in the presence of ulceration.

In the cases of combined thromboangiitis obliterans and arteriosclerotic peripheral vascular disease, the adhesive count usually fell into the range of the cases of arteriosclerotic disease, since by the time these patients reached the age of development of arteriosclerosis, the activity of the thromboangiitis obliterans process had subsided.

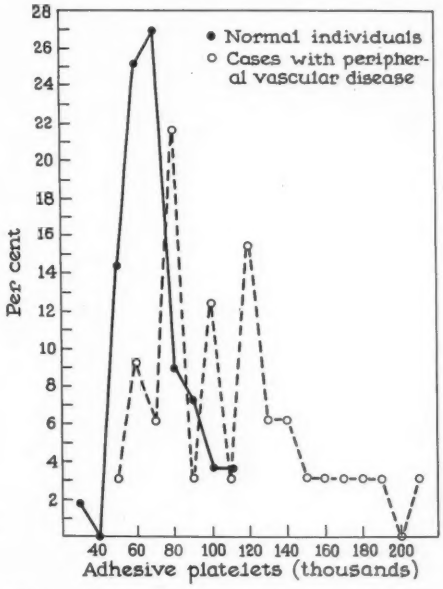

FIG. 1. Chart showing record of normal patients and patients with arteriosclerosis obliterans, thromboangiitis obliterans, acute thrombophlebitis and chronic venous insufficiency.

DISCUSSION

In our series of 12 cases of coronary thrombosis on which fifty-five serial tests were performed we were unable to confirm the findings of Moolten and associates[3–5] concerning the rise and fall of adhesive platelets in this condition.

Anticoagulant therapy in the form of dicumarol was found to produce a marked decrease in the adhesive platelet count in active cases of thromboangiitis obliterans. When dicumarol was discontinued, the adhesive count rose sharply. This differs from the work

of Moolten and associates, who found little effect on platelet adhesiveness from dicumarol therapy.

As stated by Moolten and co-workers,[3–5] marked platelet hyperadhesiveness predisposes to thrombosis. This is a generally accepted fact. It is of interest that we found such hyperadhesiveness in active thromboangiitis obliterans and in acute deep thrombophlebitis but not in coronary thrombosis or arteriosclerotic peripheral vascular thrombosis. Possibly this may assist in differentiating these two types of peripheral vascular disease in doubtful cases.

All previous laboratory tests done on patients with thromboangiitis obliterans, including a variety of blood chemistry studies, have revealed no difference in the blood of these patients when smoking and not smoking. Patients with this disease who continue to smoke have a progressive disease, whereas in those who have stopped smoking, the disease becomes completely arrested. In patients with thromboangiitis obliterans who smoke, we found an increase in platelet adhesiveness, which falls with cessation of smoking.

Summary and Conclusions

(1) Four hundred and ninety-seven adhesive platelet tests were performed in this study.

(2) Two hundred of these tests were made on over 100 normal individuals. The normal adhesive platelet count was found to be between 42,000 and 72,000.

(3) Two hundred and thirty-two tests were performed on 125 cases of peripheral vascular disease which included thromboangiitis obliterans, 35 cases; arteriosclerotic peripheral vascular disease, 60 cases; arteriosclerotic heart disease, 12 cases; thrombophlebitis, 7 cases; miscellaneous disease, 12 cases.

(4) Fifty-five tests on 12 cases of acute myocardial infarction did not reveal any abnormal response in platelet adhesiveness.

(5) Serial tests on 5 cases of lupus erythematosus disseminatus treated with cortisone did not reveal any change in total or adhesive platelet counts.

(6) Sustained hyperadhesiveness of platelets was found only in thromboangiitis obliterans and thrombophlebitis; this may be used as an aid in differential diagnosis.

(7) Dicumarol produces a decidely marked decrease in platelet adhesiveness.

(8) Cigarette smoking does not affect platelet adhesiveness in normal individuals or those with arteriosclerotic peripheral vascular disease.

(9) Cessation of cigarette smoking in 5 cases of thromboangiitis obliterans which we tested resulted in a very significant decrease in platelet adhesiveness.

(10) This is the first biologic test which has shown a difference in patients with active and inactive thromboangiitis obliterans.

Acknowledgments

We wish to express our appreciation to Dr. Nathan Rosenthal and Dr. Samuel Silbert for their help and guidance in preparing this report.

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The Effect of Salt Loading and Salt Depletion on Renal Function and Electrolyte Excretion in Man

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With the Technicalh Assistance of Martha Barrett and Bernice Dumas

Glomerular filtration rate (GFR), renal plasma flow (RPF), and electrolyte excretion were studied in 17 patients subjected to salt depletion and loading. Salt depletion led to maximal renal salt conservation with the average GFR and RPF slightly decreased. Salt loading produced increased excretion of sodium and chloride with the average GFR and RPF slightly increased. Since the decreased electrolyte excretion with salt depletion and increased electrolyte excretion with salt loading were essentially independent of the direction of change in GFR and RPF, it is inferred that tubular absorptive activity is a more significant factor in achieving electrolyte balance than are GFR changes.

GENERALIZED accumulation of edema fluid is primarily a consequence of the incapacity of the kidneys to eliminate salt as rapidly as it is absorbed from the intestinal tract.[1] The retention of sufficient water to form an isotonic solution creates a vascular plethora which favors diversion of fluid from the blood stream to the interstitial spaces.[2] The normal individual retains fluid and gains weight only if salt intake is greatly increased, whereas the potentially edematous patient tolerates but minimal quantities of salt without abnormal expansion of extracellular fluid volume.

Electrolyte balance is maintained by the excretion each day of somewhat less than 1 per cent of the salt which is filtered through the glomeruli; over 99 per cent is absorbed by the renal tubules. If salt intake is quadrupled, balance can be preserved by the elimination of what is still a relatively insignificant proportion of the filtered moiety. The means by which the normal kidney effects this increased salt excretion is imperfectly understood, as is the nature of the renal defect in the edematous patient which prevents a similar compensation.

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This work was supported by a grant from the Life Insurance Medical Research Fund.

It is theoretically possible that salt elimination might be increased primarily by a reduction in the salt absorptive capacity of the renal tubules, or secondarily by such an increase in the rate of glomerular filtration that more salt would be delivered to the tubules than could be absorbed. The present study on normal man was undertaken to distinguish between these two possibilities. It has been observed that salt excretion is increased on salt loading by a decrease in the tubular absorption of salt independent of any change in filtration rate. However, it appears that the excess salt is eliminated more rapidly if an increase in filtration rate delivers increased quantities of salt into the renal tubules.

METHODS

The study described in this paper is based on 150 clearance observations on 17 convalescent patients from the medical wards of the University Hospital. Except for 2 patients with an incidental clinical diagnosis of mild hypertension and 2 with cirrhosis without ascites or edema, patients with cardiorenal disease or disturbances of fluid balance have been excluded from the present report.

Two types of experimental procedure have been employed in attempting to assess the relative roles of changes in glomerular filtration rate and tubular absorptive activity in the maintenance of fluid and electrolyte balance. In the first series of experiments, control measurements of filtration rate, plasma flow and clearance of sodium, potassium and chloride ions were made in a state of normal hydration dur-

ing a period in which the patient was maintained on the routine ward diet. Subsequently, the patient was salt depleted by the restriction of salt intake and the intravenous administration of 2 cc. of Mercuzanthin per day for three days. On the fourth day the measurements were repeated. The patient was then salt loaded by the intravenous administration of 3 liters of 0.9 per cent saline each day for three days. Again on the fourth day the measurements were repeated. In all, 5 patients were subjected to the complete series of three tests. Four additional patients were subjected to the control test and either the depletion or loading procedure. Throughout all control, salt depleting or salt loading periods water intake was unrestricted. Each test consisted of three clearance periods approximately 20 minutes in length. All were performed in the postabsorptive state 14 to 18 hours after the last meal and were preceded by the ingestion of 1 liter of water to ensure an adequate flow of urine. Inulin and paraaminohippurate were administered by intravenous drip.

In the second series of experiments, changes in renal function in response to rapid salt loading were assessed in the following manner. Control levels for filtration rate, plasma flow and clearance of sodium, potassium and chloride ions were established in three initial clearance periods, following which 1800 cc. of either 0.9 per cent saline or balanced salt solution* were administered intravenously at a rate of approximately 30 cc. per minute. During this infusion interval three additional clearance periods were obtained. Subsequent to the loading procedure a third group of three clearance periods completed the experiment. This routine was applied in 8 patients, on one of whom two experiments were performed, the first with saline, the second with the balanced salt solution.

Methods employed include that of Harrison[3] for inulin, that of Bratton and Marshall[4] for paraaminohippurate, that of Sendroy[5] for chloride, that of Van Slyke and Neill[6] for bicarbonate, and that of Phillips and associates[7] for plasma protein. Hematocrits were measured in Wintrobe tubes and analyses of sodium and potassium were performed with an internal standard flame photometer accurate to ±2 per cent.

Results

The Effect of Salt Depletion and Salt Loading on Renal Function and Electrolyte Excretion.

The clearance data on the 5 patients in which the full series of control, depletion and loading tests were completed are summarized in table 1. The control values for glomerular filtration rate, renal plasma flow and filtration fraction in these patients averaged 128 cc. per minute, 596 cc. per minute and 0.22, respectively. With the possible exception of those cited for patient Y. M., all renal variables lie within the generally accepted ranges of normal.[8]

As a result of salt depletion by three successive daily doses of Mercuzanthin, body weight decreased significantly in each subject, the average weight loss amounting to 8.3 pounds. It is apparent from the mean increase in plasma protein concentration of 0.47 Gm. per hundred cc. that only a small fraction of the lost fluid was derived from the blood plasma; the major fraction must have been derived from the interstitial and intracellular reservoirs. On an average, glomerular filtration rate decreased 4 cc. per minute and renal plasma flow decreased 44 cc. per minute. These changes are rather insignificant, especially in view of the fact that in 2 subjects (Y. M. and N. S.) filtration rate actually increased and in only one (L. B.) was the decrease appreciable.

Significant decreases in the plasma concentrations of chloride and sodium were noted in all subjects. Since chloride fell somewhat more than sodium, a rise in plasma carbon dioxide content would be anticipated and was actually observed in the 2 instances in which it was measured. Most striking, however, was the negligible clearance of chloride and of sodium, the marked conservation of these ions constituting an effective renal compensation for depleted reserves and reduced plasma levels.

As a result of salt loading by the administration of 3 liters of saline intravenously per day on three successive days, body weight increased appreciably over the control value in all but one subject, L. B. The average increase amounted to 6.7 pounds. As indicated by the decrease in protein concentration, plasma volume was somewhat increased. On an average, glomerular filtration rate increased 6.1 cc. per minute and renal plasma flow increased 26 cc. per minute. These changes are of minor significance in view of the fact that both variables actually decreased in two subjects. Further-

* The balanced salt solution contained per liter 141 millimols of sodium, 5 millimols of potassium, 119 millimols of chloride and 27 millimols of bicarbonate. It was equilibrated with 5 per cent carbon dioxide in oxygen prior to administration.

more, subject N. S. accounted for most of the average change.

Increases in the plasma concentration of sodium and chloride were noted in all subjects. in all subjects, a fact which accounts for the small weight gain in response to saline infusion, added dietary salt and free access to water.

The data relating sodium excretion to filtra-

TABLE 1.—*Clearance Data for Control, Salt Depletion, and Slow Salt Loading Periods*

Patient	Diagnosis	Regimen	Blood Press.	Wt.	Urine Flow	Glom. Filt. Rate	Renal Plasma Flow	Filt. Frac.	Plasma Concentration					Clearance		
									Na	K	Cl	CO_2	Prot.	Na	K	Cl
			mm. Hg	lbs.	cc. per min.				m.Eq. per liter				Gm. %	cc. per min.		
Y. M.	Psycho-	Control	112/75	151	7.17	93.2	389	0.24	142.6	4.35	110.0		7.52	1.14	19.5	1.25
F.	neuro-	3 × 2 cc. Mercuzan.	122/81	143	2.89	101.4	373	0.27	134.5	4.49	98.0		8.25	0.04	8.8	0
49 yrs.	sis	3 × 3 liters NaCl	122/72	169.5	9.89	98.0	419	0.23	144.0	4.24	115.8		6.11	2.30	11.8	2.79
M. W.	Cirrho-	Control	122/90	118	3.26	127.2	599	0.21	139.1	3.45	108.0	25.6	8.33	0.82	6.3	0.74
F.	sis	3 × 2 cc. Mercuzan.	116/89	111.5	4.18	123.5	578	0.21	134.2	3.95	98.8	27.4	9.24	0.04	5.3	0
32 yrs.		3 × 3 liters NaCl	140/103	123	3.40	125.2	521	0.24	141.1	3.64	113.3	22.8	7.04	1.35	6.3	1.46
H. S.	Peptic	Control	130/89	189	14.6	144.0	725	0.20	141.9	4.41	109.7	26.0	7.96	1.97	29.2	1.77
M.	Ulcer	3 × 2 cc. Mercuzan.	117/82	178	7.87	138.2	626	0.22	136.6	4.09	101.4	27.9	8.51	0.20	16.0	0.03
36 yrs.		3 × 3 liters NaCl	131/95	193	11.9	148.7	701	0.21	142.5	4.21	112.4	24.0	7.51	4.07	15.0	4.97
N. S.	Peptic	Control	99/69	171.5	3.05	128.2	620	0.21	139.6	4.96	104.5		7.22	0.43	29.4	0.69
M.	Ulcer	3 × 2 cc. Mercuzan.	99/61	160	2.79	129.0	587	0.22	136.0	4.12	103.9		6.93	0.02	23.8	0.03
43 yrs.		3 × 3 liters NaCl	112/72	179	9.46	152.5	789	0.19	140.6	3.60	107.8		6.86	2.97	31.1	3.06
L. B.	At.	Control	120/64	130	1.43	148.0	649	0.23	138.8	4.12	108.1		6.78	0.41	21.1	0.42
M.	Pneu-	3 × 2 cc. Mercuzan.	113/77	125.5	1.36	131.0	594	0.22	136.8	3.32	104.4		7.22	0.05	21.0	0
14 yrs.	monia	3 × 3 liters NaCl	121/71	128.5	4.27	146.6	682	0.22	142.1	4.09	110.5		6.56	2.74	17.5	3.08

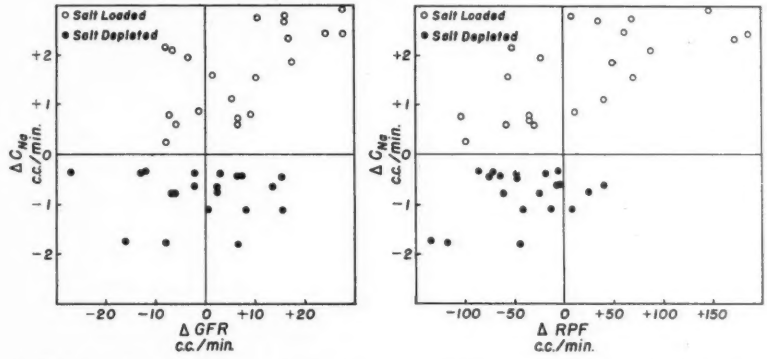

FIG. 1. Relationship of sodium clearance to glomerular filtration rate and renal plasma flow (salt loading).

Since chloride increased more than sodium, a fall in plasma carbon dioxide content would be expected and was actually observed in the 2 subjects in which it was measured. The clearances of chloride and of sodium were increased

tion rate and plasma flow derived from all 23 experiments, including those in which a complete as well as an incomplete series of tests were performed, are summarized in figure 1. The change in sodium clearance relative to the

control value is plotted against the change in glomerular filtration rate and against the change in renal plasma flow. The data clearly fall into two groups. The sodium clearance was reduced relative to normal in all salt depleted subjects, independent of change in filtration rate or plasma flow. The sodium clearance was increased relative to normal in all saline loaded subjects, independent of change in filtration rate or plasma flow. Obviously, the differences

TABLE 2.—*Clearance Data for Two Experiments on Patient E. B. for Control and Rapid Salt Loading Periods*

Patient	Diagnosis	Elapsed Time	Blood Press.	Urine Flow	Glom. Filt. Rate	Renal Plasma Flow	Filt. Frac.	Plasma Concentration					Hct.	Clearance		
								Na	K	Cl	CO_2	Prot.		Na	K	Cl
		min.	mm.Hg.	cc. per min.				m.Eq. per liter				Gm. %	%	cc. per min.		
Experiment 1																
E. B. 47 yrs. 180 lbs. 5′6″	Convalescent Pneumonia. Mild Cirrhosis	31–51	130/88	10.20	150.2	610	0.25	138.3	4.23	109.0	25.1	7.29	45.3	1.47	17.0	1.49
		51–71	125/90	7.80	141.4	541	0.27	140.0	4.23	109.4				1.61	16.5	1.58
					145.8	576	0.26							1.54	16.8	1.54
		82–147 1800 cc. 0.9 per cent Sodium Chloride at 27.7 per min.														
		71–101	130/95	5.77	131.4	530	0.25	140.4	4.23	109.6		6.93	44.2	1.81	17.8	1.81
		101–122	145/100	9.37	152.8	664	0.23	141.3	4.11	112.3		6.56	42.2	2.84	20.8	2.86
		122–142	140/90	10.53	139.3	642	0.22	140.0	4.07	112.7	22.8	6.48	41.6	3.24	17.1	3.56
					141.2	606	0.23							2.63	18.6	2.74
		142–167	130/90	10.82	131.8	583	0.23	142.1	4.07	112.3				4.00	18.4	4.52
		167–187	140/95	5.20	125.4	492	0.26	141.3	4.23	113.3				3.02	18.8	3.59
		187–207	140/95	3.80	126.5	493	0.26	141.7	4.23	112.7	23.4	6.78	43.0	2.64	17.7	3.16
					127.9	523	0.25							3.22	18.3	3.76
Experiment 2																
E. B.		32–55	115/75	7.18	152.0	628	0.24	139.6	4.52	107.4	22.9	7.89	45.4	0.66	17.7	0.96
		55–76	115/75	5.52	140.0	556	0.25	139.6	4.36	107.8				0.76	17.0	1.00
					146.0	592	0.24							0.71	17.4	0.98
		78–134 1800 Balanced Salt Solution at 32.2 cc. per min.														
		76–99	135/90	5.65	140.0	610	0.23	140.8	4.11	109.7		6.93	43.0	1.87	23.5	2.14
		99–117	140/95	10.12	146.0	729	0.20	142.1	4.11	111.2		6.56	40.7	3.78	46.0	4.23
		117–143	140/95	14.62	142.0	660	0.22	142.1	3.95	111.2	25.7	6.49	40.5	5.60	50.8	6.37
					143.0	666	0.22							3.75	40.1	4.25
		143–164	140/95	3.90	112.0	446	0.25	143.7	4.03	109.3				3.39	33.7	4.18
		164–186	140/95	2.77	125.0	522	0.24	142.9	3.95	110.6				3.33	27.6	3.58
		186–207	150/95	2.88	146.0	664	0.22	142.9	3.87	110.4	27.0	6.86	43.0	3.86	18.9	4.35
					128.0	544	0.24							3.52	26.7	4.04

in sodium clearance between the states of dehydration, normal hydration and saline loading cannot in these experiments be related primarily to changes in either filtration rate or plasma flow. They must be due in large part to alterations in completeness of tubular absorption of sodium. However, in the data obtained after saline loading there appears to be a relationship between the magnitude of the increase in sodium clearance and both filtration rate and plasma flow, imperfect though the correlation may be.

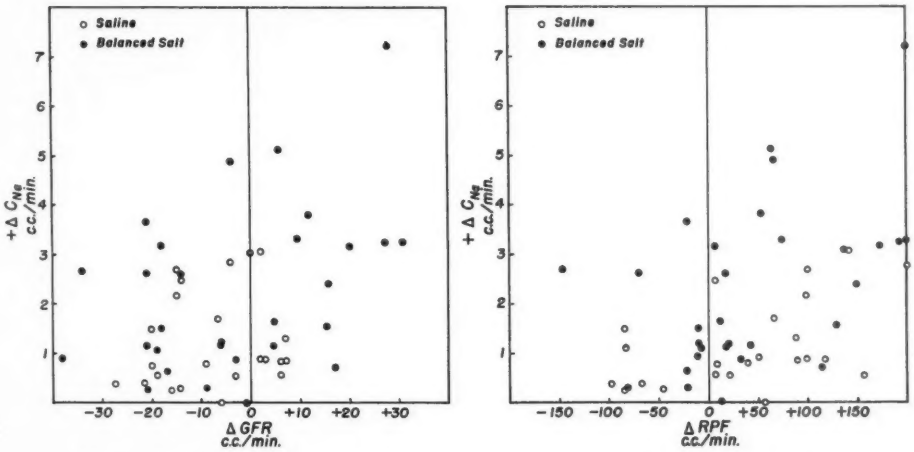

FIG. 2. Relationship of sodium clearance to glomerular filtration rate and renal plasma flow (rapid salt loading).

The Effect of Rapid Hydration on Renal Function and Electrolyte Excretion.

The nine experiments in which patients were rapidly hydrated with 1800 cc. of either normal saline or balanced salt solution confirm the above expressed view that major changes in electrolyte clearance may be effected by alterations in tubular activity independent of changes in renal plasma flow and filtration rate. Two experiments on one subject, E. B., are summarized in table 2. It is apparent from both plasma protein concentration and hematocrit that rapid hydration with saline (experiment 1) produced a significant degree of hemodilution. During the infusion a slight increase in renal plasma flow occurred; filtration rate actually dropped. However, both variables were reduced below the normal in the posthydration period. Despite these facts the clearance of sodium and chloride increased, although the increase was not especially striking. Essentially the same response was observed in experiment 2, in which the balanced salt solution was administered. Two differences are, however, worthy of note. Sodium and chloride clearances increased slightly more with the infusion of the balanced salt solution than with the saline. Although the differences are small, they have been observed repeatedly in both man and dog. The potassium clearance in the experiment with the balanced salt solution which contained 5 millimols per liter of potassium chloride, was much increased, indeed to such an extent that an actual fall in plasma potassium concentration resulted.

The data relating sodium excretion to filtration rate and plasma flow in all nine experiments in which 1800 cc. of fluid were rapidly infused are summarized in figure 2. The change in sodium clearance during and after the infusion relative to the average of the three control values is plotted against the change in glomerular filtration rate or plasma flow. It is apparent that the sodium clearances in all infusion and postinfusion periods with two exceptions were significantly elevated over the control values independent of change in filtra-

tion rate or plasma flow. The two instances in which no change in clearance occurred were both initial infusion periods. Obviously, the increase in sodium clearance in these experiments cannot be related directly to change in filtration rate or renal plasma flow, but must be assigned in large part to change in tubular absorptive activity. However, as was suggested in the previous series of experiments, there appears to be a significant relationship between the magnitude of the increase in sodium clearance and both filtration rate and plasma flow, imperfect though the correlation may be.

Discussion

According to Wesson and his co-workers,[9] variations in filtration rate play a prominent role in maintenance of electrolyte balance under differing salt loads. This view is based on their concept that a fixed proportion of the filtered sodium amounting to 87.5 per cent is absorbed in the proximal tubular system. The 12.5 per cent delivered into the distal tubule is ordinarily slightly more than enough to saturate the fixed and limited reabsorptive capacity of this segment. The excess is excreted. If salt load is low, the circulating blood volume is reduced and filtration rate declines. The delivery of 12.5 per cent of this reduced filtered moiety into the distal segment less than saturates its absorptive capacity and essentially all of the sodium is conserved. If salt load is high, the circulating blood volume is expanded and filtration rate increases. The delivery of 12.5 per cent of the increased filtered moiety into the distal segment more than saturates absorptive capacity and the rate of excretion of sodium rises. As salt and fluid are lost, blood volume contracts and filtration rate declines to the more normal range. Sodium excretion again returns to normal.

In support of this concept, Ladd and Raisz[10] have demonstrated in the dog a positive correlation between salt load, salt excretion and filtration rate. Furthermore, Merrill[11] and others[12–14] claim that a reduction in filtration rate without a corresponding reduction in tubular absorptive capacity underlies the sodium retention observed in chronic congestive heart failure and acute glomerulonephritis. Our data support this concept in part in that they indicate that under salt loading the magnitude of the increase in sodium clearance is greater if filtration rate increases. The fact that filtration rate ordinarily increases but little in man whereas in the dog it increases markedly may explain the relative inability of the former to eliminate rapidly a large salt load.

However, our experiments more directly confirm the view of Leaf and associates[15, 16] and Kattus and Sinclair-Smith and co-workers[17, 18] that achievement of electrolyte balance under high salt load or exercise depends primarily upon a reduction in tubular absorptive capacity. It would appear that the rate of secretion of adrenal cortical hormone varies inversely with salt load.[15] High salt load, low rate of hormone secretion and increased absorptive capacity lead to salt conservation. There is evidence suggesting that exaggeration of this latter hormonal response is the cause of salt retention in those diseases characterized by the formation of edema.[19–22] Actually, our results indicate only that variations in completeness of tubular absorption play a more significant role in determining electrolyte balance in man than do variations in filtration rate. They have no bearing on the mechanism by which this end is achieved. In the salt depleted state, the decreases in plasma sodium and chloride concentration must in themselves largely condition the nearly complete renal conservation of these ions.

Summary

Glomerular filtration rate, renal plasma flow and electrolyte excretion have been studied in a series of 17 convalescent patients subjected to salt depleting and salt loading procedures in an attempt to assess the relative roles of changes in glomerular filtration and tubular absorptive activity in the maintenance of electrolyte balance. When patients were salt depleted by a low salt diet and the administration of 2 cc. of Mercuzanthin per day for three days, rates of excretion of sodium and chloride were reduced nearly to zero. Glomerular filtration rate and renal plasma flow were on an average slightly decreased, but independent of the direction of change in these renal variables,

both ions were maximally conserved. The plasma levels of sodium and chloride were reduced by such salt depleting measures and the filtered ion loads decreased. It is inferred that a lower filtered load favors more complete absorption. When patients were salt loaded gradually by the administration of 3 liters of saline per day for three days or rapidly by the infusion of 1800 cc. of saline in one hour, sodium and chloride excretion were increased. Although glomerular filtration rate and plasma flow were on an average slightly increased, sodium and chloride clearances were elevated independent of the direction of change in these renal variables. It is inferred that a decrease in tubular absorptive activity under salt loading is a more significant factor in achieving electrolyte balance than is an increase in glomerular filtration rate. However, the magnitude of the increase in electrolyte excretion which results from salt loading appears to be related directly to filtration rate.

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Visualization of the Coronary Arteries during Life

By James A. Helmsworth, M.D., Johnson McGuire, M.D., Benjamin Felson, M.D., and Ralph C. Scott, M.D.

By retrograde catheterization of the carotid or the brachial arteries small polyethylene or woven catheters have been inserted into the ascending aorta in 10 individuals. Diodrast or Neo-Iopax solution was forcibly injected and serial roentgenograms were rapidly taken. The coronary arteries or branches were demonstrated in 5 of the subjects. Similar studies were made in 5 dogs with normal hearts, and also in 10 dogs in whom a coronary artery had previously been obstructed. In certain of the normal animals not only the larger, but also smaller branches were clearly shown and the absence of filling in obstructed vessels was demonstrated.

ROENTGEN visualization of the coronary arteries in the living patient would contribute greatly to the diagnosis of coronary artery disease. It also should be helpful in studying the results of experimentally induced coronary obstruction in animals. With these objectives in mind, a technic of coronary arteriography which has proved successful in animals and in man is presented.

In an earlier communication[1] a method of visualization of the coronary arteries was described. A radiopaque medium was injected through a catheter inserted via the brachial artery into the ascending aorta and the coronary arteries were demonstrated roentgenographically. These studies have been continued and, to date, successful visualization of the coronary arteries in 13 dogs and 5 human beings has been obtained. The purpose of the present report is to describe the technic and hazards of coronary arteriography and to record additional experiences in this field.

Rousthöi,[2] in 1933, filled the coronary arteries in living rabbits by inserting a catheter into the ascending aorta via the common carotid artery and injecting Thorotrast. Grossman,[3] employing a similar method, visualized the coronary arteries with Diodrast in 5 dogs. Recently, Pearl and his co-workers[4] reported coronary visualization with Diodrast in dogs, using a special nylon catheter. Barclay and co-workers[5] visualized the coronary circulation in a viable sheep fetus by retrograde injection through the femoral artery. Hoyos and Del Campo[6] obtained coronary artery filling with Diodrast in man by needle puncture of the ascending aorta through the anterior chest wall. Gordon, Brahms, and Sussman[7] noted incidental filling of the coronary arteries in 10 of 1200 angiocardiograms. In 1948, Jönsson,[8] using the method of catheter aortography which he attributed to Radner,[9] successfully visualized the coronary arteries in 5 human subjects.

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Technic

Preliminary experiments were carried out on 15 dogs. The anesthetic agent was intravenous sodium pentobarbital. A segment of the right common carotid artery was mobilized and a serrefine clamp was placed on the distal extremity of the mobilized segment. A looped sling of fine silk was then placed about the proximal extremity. Through a small transverse incision in the artery, a polyethylene or a woven cardiac catheter was advanced into the ascending aorta. At frequent intervals physiologic saline was slowly flushed through the catheter in an effort to prevent thrombosis.

Under fluoroscopic control the catheter was advanced to approximately 1 cm. above the aortic valve. Contrast substance was injected to the tip of the radiolucent polyethylene catheter in order to identify its position. Early in the study single Bucky roentgenograms were made immediately following the rapid (0.2 to 0.8 second) injection of varying amounts (7 to 15 cc.) of 70 per cent Diodrast or 75 per cent Neo-Iopax. As many as 16 injections were given to one animal. Later, serial roentgenograms were made

at one-half second intervals during and following the injection using the Fairchild Roll Film Cassette.* With this apparatus fewer injections were necessary. In the later experiments electrocardiographic tracings were taken before, during, and after the injection of the contrast agent. At the completion of each study the carotid artery was ligated and a simple wound closure made.

Ten animals were specially prepared by ligation and division of a branch of the left, right, or circumflex coronary artery. The ends of the severed vessel were marked with silver clips to permit their identification on roentgenograms. Coronary arteriography was then performed, usually within six hours after the occlusion. Four animals were sacrificed after coronary arteriography. The heart was removed and injected intact, using a modification of the Schlesinger technic.[10]

After these preliminary animal experiments, coronary arteriography was carried out on patients. Premedication consisted of morphine and sodium pentobarbital in dosages depending upon the weight of the patient. Food and water were withheld for six hours before the study. No anticoagulant was administered. An ocular test for sensitivity to the contrast agent was made. Experience demonstrated that the right brachial, the right common carotid, and either of the superficial femoral arteries were best suited for the passage of the catheter into the ascending aorta. Under local anesthesia the artery was exposed through a small incision and a 4 cm. segment was mobilized by dividing and ligating only the smallest branches. After the adventitia was removed a looped sling of silk was placed around the extremities of the segment. A transverse opening was made in the vessel and tension on the slings prevented blood loss. As the catheter was inserted the proximal sling was released. The catheter was advanced under fluoroscopic control until its tip was in the proximity of the aortic valves. Continuous slow injection of saline-heparin solution (75 mg. heparin per liter of normal saline) was maintained. A final test for sensitivity was made by injecting 1 cc. of contrast medium through the catheter. From 10 to 20 cc. of 70 per cent Diodrast or 75 per cent Neo-Iopax were injected rapidly (0.8 to 2.0 seconds). In the earlier studies a single Bucky exposure was made at the end of each injection. Later, employing the Fairchild Cassette, exposures were made at one-half second intervals during and after the injection. Both common carotid arteries were digitally compressed during the injection in an effort to limit the amount of contrast agent entering the cerebral circulation. Several injections were made in each patient. Electrocardiograms were taken before, during, and after the injection in 2 cases. At the completion of the procedure the catheter was withdrawn and the vessel carefully examined. In several cases a soft thrombus was extruded before normal flow occurred from above and below the arteriotomy. The opening in the artery was closed with an everting stitch of 5-0 silk on an atraumatic needle.

*Manufactured by Fairchild Camera and Instrument Corporation, Jamaica, New York.

Results in Dogs

Coronary artery visualization was attempted in 15 dogs. In 13, successful filling (fig. 1) was obtained on one or more occasions. Repeated injections were carried out in several animals before successful coronary arteriograms were obtained. In the other 2 animals the coronary tree could not be visualized because it was impossible to pass the catheter tip into the ascending aorta.

A branch of one of the coronary arteries had been ligated in 10 of the 15 dogs studied. The site of obstruction was identified in 6 animals by visualization of the artery to the point of ligation with no filling beyond (figs. 2 and 3). In 4 animals filling was inadequate for demonstration of the occlusion. Electrocardiographic tracings were made in 9 of these 10 animals, and arrhythmias developed in 8. The arrhythmias consisted of second degree atrioventricular block, sinus arrest with nodal escape, premature ventricular contractions, paroxysmal ventricular tachycardia, and ventricular fibrillation. Changes in the T waves were observed in 5 of these animals following the injection of contrast medium. These changes consisted of increase in depth of a negative T wave, decrease in height of an upright T wave, or change of the T waves from positive to negative. These alterations were usually transient.

There were 15 attempts to visualize the coronary tree in these 9 animals. In 9 of the 11 successful injections and in 3 of the 4 unsuccessful ones arrhythmias were observed. There were T wave changes in 4 of the 11 successful injections and in 3 of the unsuccessful ones. It was therefore apparent that electrocardiographic changes developed in the absence of coronary opacification.

Electrocardiograms were made in only 1 of the 5 normal dogs and no arrhythmia was seen although transient T wave changes were noted. Twenty cc. of physiologic saline were rapidly injected through the catheter in 4 of the ani-

mals and no electrocardiographic changes were observed.

Five deaths occurred in the entire group of 15 animals. These fatalities were encountered in animals in which recent coronary ligation had been performed. Three developed frequent premature ventricular contractions following the coronary artery ligation and died of ventricular fibrillation shortly after the injection. The other 2 died several hours after the procedure, the cause of death being undetermined.

Results in Man

Coronary visualization was attempted in 10 patients with successful filling in 5. In 3 cases the demonstration of the coronary arteries was good (figs. 4 and 5), while in the remaining 2 cases the filling was less complete.

Electrocardiographic observations were made during attempts at coronary visualization in 2 patients. Successful filling in 1 patient was associated with a brief period of sinus slowing. In the other patient, although no contrast medium was demonstrated in the coronary tree, there was transient increase in the height of the T waves immediately following the injection.

Discussion

It has been possible to demonstrate one or more major vessels as well as a number of the smaller branches of the coronary tree in both dogs and patients. In certain instances the left coronary artery was better filled and in others the right. It is believed that the factor determining which vessel will fill best with a given injection is the location of the tip of the catheter in relation to the orifice of the vessel. Visualization of the coronary tree in the dogs was invariably clearer than in the human beings. Technically, the quality of the films was better in the animals because of their smaller mass. Furthermore, a larger quantity of contrast medium was injected proportionately in the animals than in the humans.

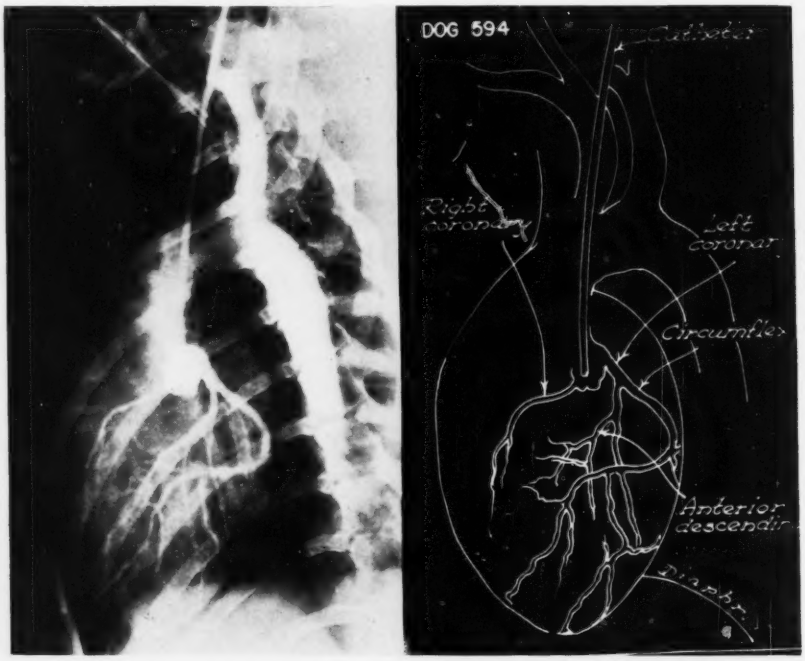

Fig. 1. Dog 594. Coronary arteriogram, right posterior oblique view. Note the filling of all the major coronary arteries and many of the smaller branches.

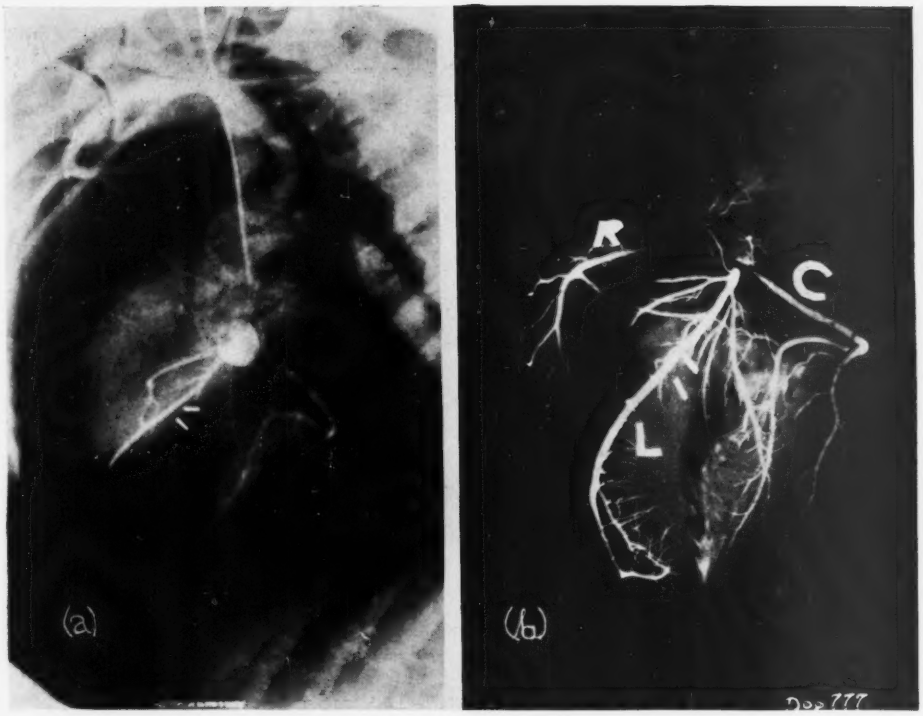

FIG. 2. Dog 777. (*a*) Coronary arteriogram, right posterior oblique view. (*b*) Postmortem injected specimen in same position. *R*, right coronary artery. *L*, left anterior descending artery. *C*, circumflex artery. The site of occlusion is marked by the proximal metallic clip.

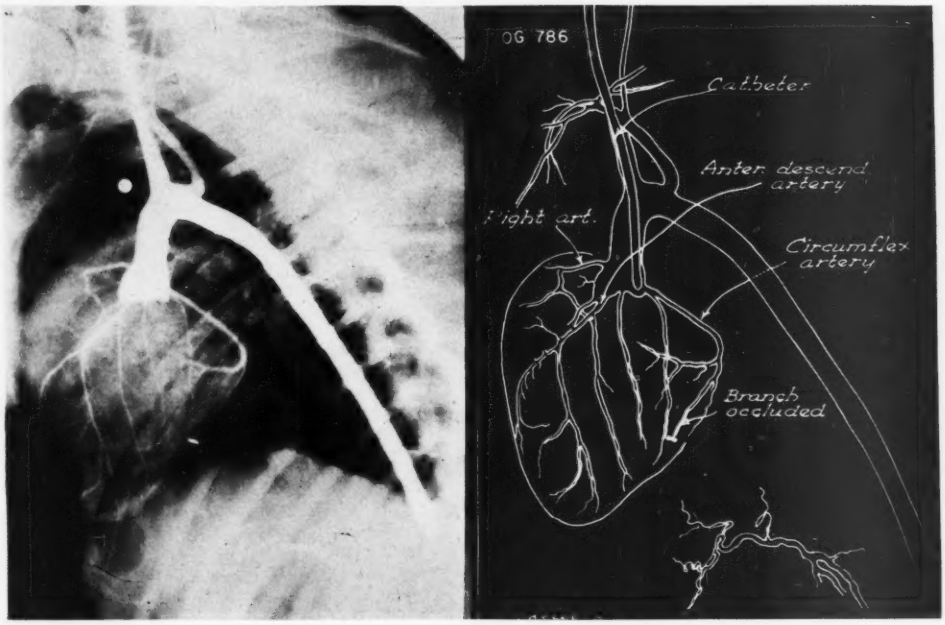

FIG. 3. Dog 786. Coronary arteriogram, right posterior oblique view. The site of occlusion of a branch of the circumflex artery is indicated in the roentgenogram and tracing by the metallic clip. The round metallic object at the level of the aortic arch was a buckshot.

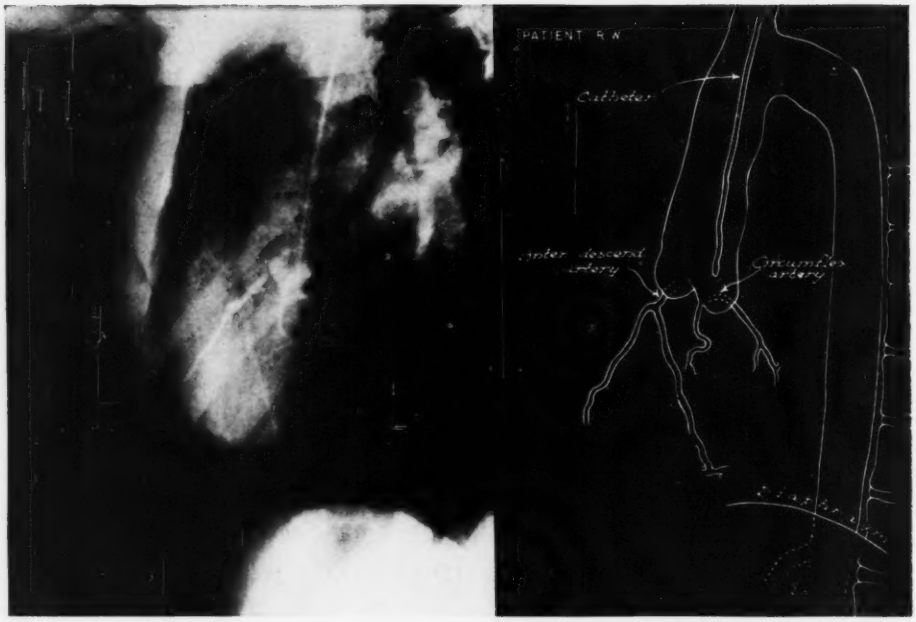

FIG. 4. Patient R. W. Diagnosis: mediastinal tumor. Coronary arteriogram, right posterior oblique view. Note filling of the anterior descending and circumflex arteries.

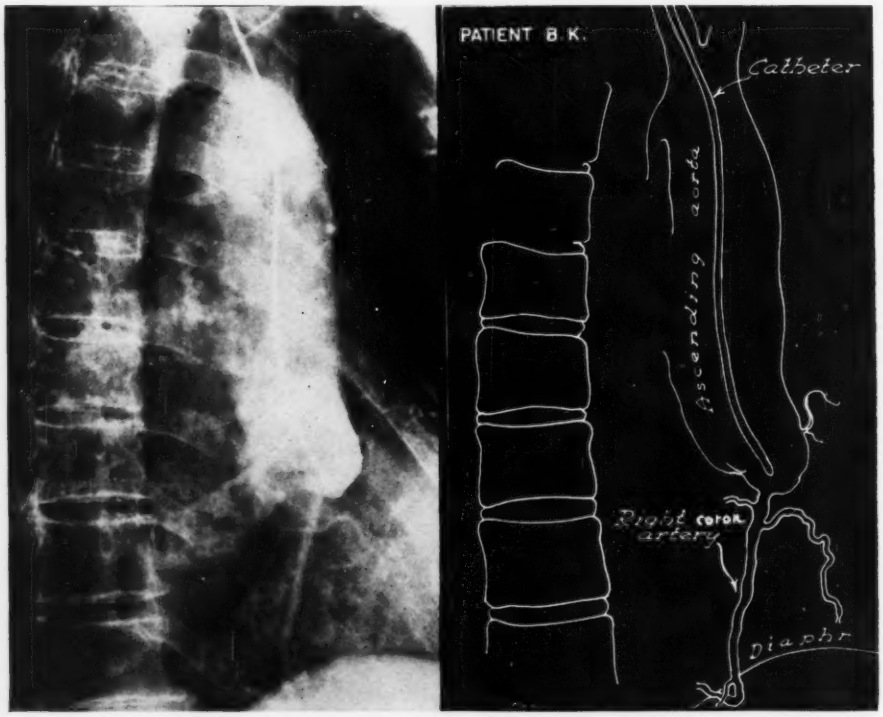

FIG. 5. Patient B. K. Left posterior oblique view. Note that the anterior descending and circumflex arteries did not fill. Autopsy showed marked arteriosclerotic narrowing of these vessels. The right coronary artery was essentially normal.

The possibility that coronary arteriography may prove of value in the detection of coronary artery disease is suggested by the demonstration of the site of occlusion in the animals prepared by coronary ligation. This is further suggested by the failure of the left coronary artery to fill in patient B.K. (fig. 5), related, in our opinion, to the extensive arteriosclerotic narrowing found in this vessel at autopsy.

The most important consideration in coronary arteriography is its effect upon the patient. Jönsson[8] noted no reactions in 5 patients in whom the coronary arteries were filled. In our group of 10 patients there was 1 fatality which has been previously reported.[1] This occurred in an 88 year old moribund woman who died suddenly after the sixth injection of 10 cc. of 70 per cent Diodrast. This was one of the early cases and since that time no significant reactions have been encountered. In Grossman's experiments[3] 4 out of 5 dogs succumbed to the procedure. In our 15 animals there were 5 deaths which were attributed to the arteriography. Each death occurred in an animal who had been subjected to thoracotomy with coronary ligation a few hours earlier.

The 2 patients who had electrocardiograms taken during the procedure developed no arrhythmias. All the dogs that developed arrhythmias had had coronary ligation. It is to be noted that no electrocardiographic abnormalities were found in normal dogs during the procedure as performed by Pearl and his coworkers.[4]

The contrast substances used in this study were 75 per cent Neo-Iopax and 70 per cent Diodrast. No sensitivity reactions were encountered. Because of the reactions of blood vessels to these concentrated media, it is felt that neither of them is ideal for coronary arteriography. The dangers of the method would be reduced if a safer contrast medium were found. It seems likely that the arrhythmias following the injection of Diodrast or Neo-Iopax are due to vasospasm, anoxia or direct irritation of the myocardium.

The polyethylene catheter has been very useful because of the thinness of its wall, which permits a larger bore to be inserted into the artery. It has the disadvantage of being radiolucent. It was noted that arterial spasm occurred unless a catheter was used which moved freely and without friction in the artery. Thrombosis of the incised artery did not occur in any patient.

Prior to the use of the Fairchild Roll Film Cassette one Bucky film was made at the end of each injection and multiple injections were often necessary to obtain visualization of the coronary arteries. Since using the Fairchild Cassette fewer injections have been required since films made at one-half second intervals for a period of four seconds are more likely to depict the brief period of coronary opacification.

Summary

1. The coronary arteries in man and dogs have been visualized roentgenographically by catheterization of the ascending aorta and injection of radiopaque media.

2. The site of experimentally produced coronary occlusion in dogs has been demonstrated.

3. The hazards of the procedure are emphasized and it is recommended that, for the present, coronary arteriography should be limited to experimental investigation.

4. The method should prove of value in studying experimentally induced coronary artery disease in animals. With improved contrast agents it may prove helpful in the diagnosis of coronary artery disease in man.

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An Occupational Analysis of 580 Cardiac Clinic Patients

By THE STAFF OF THE WORK CLASSIFICATION UNIT, ADULT CARDIAC CLINIC

This report, the first of a series, presents a fairly detailed analysis of the occupational status of a group of cardiac clinic patients as found at a single point of time. An analysis of this type sheds little or no light on the effects of occupation on the course of heart disease, but it does give some indication of the extent to which cardiacs can carry on useful activities.

THE GROWING importance of heart disease as a possible cause of restricted physical exertion has created a demand for information relating to the ability of persons with heart disease to carry on useful and productive activity. Since 1920 a number of published articles have attempted to shed light on this subject.[1–8] Unfortunately, most of the reports merely present the opinions of the authors; few contain data that will stand up under careful scrutiny. Perhaps the two most serious defects have been (1) failure to utilize accepted criteria and nomenclature in the diagnosis of heart disease, and (2) absence of long-term observations on cardiac status in relation to occupational status.

In 1944, Kresky and Goldwater[9] published a detailed analysis of the occupational activities of 2,081 patients who in 1941 were attending ten cardiac clinics affiliated with the New York Heart Association. This report revealed, among other things that 84 per cent of 1,062 females and 47 per cent of 1,019 males were working at the time of the study. It is obvious that an analysis of the occupational status of a group of cardiac patients at any single point of time is of limited value since it provides no information on the effects of occupation on the course of heart disease. Nevertheless this type of "spot check" does give some indication of the proportion of persons with heart disease who are able to find and retain employment, and also can show the variety of occupations in which individuals with all types and with all degrees of severity of heart disease may be engaged. It should be borne in mind that this analysis does not show ability to work, since many more of the patients might have been employed if suitable jobs could be found for them. In this regard, the state of the labor market may be more important than the state of the heart. Furthermore, there may be many cardiac patients, particularly those classified as IIIC or poorer, who are too sick even to attend a cardiac clinic and others who do not attend clinic until they develop a disability which prevents their working. Thus the present sample cannot be said to be necessarily representative of heart patients in general.

Although the present study follows the same general lines as that done in 1941, it differs in that it includes a more detailed analysis of occupations than was made in the earlier investigation, consequently a brief report seems to be justified. This report is not presented as a controlled study since no attempt was made to compare the cardiac clinic patients with those attending other clinics because of other acute or chronic illnesses. It is hoped that such a comparison may be made at a future time and also that information may become available on the occupational status of "normal" individuals

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The following members of the staff have contributed to the work which forms the basis for the reports: Doctors Herman Bennett, Anthony Brittis, Lewis Bronstein (Associate Chief of Unit), Sigmund Falk, John Iselin, Leonard Goldwater (Chief of Unit), Beatrice Kresky, Warren Lacey, Otakar Machek, Sol Parent, Samuel Sverdlik, Gerald Weinberger, Jean Wolfson; Martha Ashcraft (Administrator), Lois Mills (Research Assistant), Gladys Nunn (Vocational Counsellor). Consultation service was provided by Dr. Adolph Berger (Associate Chief) and Dr Charles Kossmann (Chief), Adult Cardiac Clinic.

This study was aided by a grant from the New York Heart Association.

of the same age distribution as that of the cardiac group.

Composition of the Group

The group studied comprised 580 adults who were attending the Bellevue and Lenox Hill Hospital Cardiac Clinics in 1949. The sex and age composition of the group is given in table 1. Males and females were present in approximately equal numbers and slightly more than one half fell into the age group of 55 years and over. In this older age group there was a higher proportion of males than females. It may be mentioned in passing that the survey of 1941 embraced a group of which only 38 per cent had passed the 55 year mark as compared with 52 per cent in the present study.

Table 1.—*Age and Sex Distribution of 580 Patients with Heart Disease Attending Bellevue Hospital and Lenox Hill Cardiac Clinics in 1949*

Age	Sex				Total	
	Male		Female			
	No.	%	No.	%	No.	%
0–34	53	18	62	24	115	20
35–54	66	21	95	31	161	28
55 and over	189	61	115	45	304	52
Total	308	100	272	100	580	100

Table 2.—*Etiologic Classification of 580 Patients with Heart Disease*

Etiology	Age						Total	
	0–34		35–54		55 and over			
	No.	%	No.	%	No.	%	No.	%
Heart Disease Rheumatic	97	84	91	56	21	7	209	37
Heart Disease* Degenerative	2	2	48	30	250	82	299	51
Other†	16	14	23	14	32	11	72	12
Total	115	100	162	100	303	100	580	100

* Includes hypertensive heart disease, hypertensive arteriosclerotic heart disease and arteriosclerotic heart disease.

† Includes congenital heart disease, syphilitic heart disease, cor pulmonale and etiology unknown.

In respect to etiology (table 2) just over one half of the group were classified as having hypertensive and arteriosclerotic heart disease and slightly more than one third as having rheumatic heart disease with an age distribution characteristic of these etiologies.

All grades of functional and therapeutic classification were found in the group, as shown in table 3. It is of interest to note that nearly half of the cases fell into the IIC and IIIC classifications. This is of great importance since it means that we are not dealing with patients having a minimal degree of heart disease. While a majority of the cases having the less favorable functional and therapeutic classifications fell in the older age group, a substantial number was found among the younger patients.

Table 3.—*Functional and Therapeutic Classification* of 580 Patients with Heart Disease*

Functional & Therapeutic Classification*	Age						Total	
	0–34		35–54		55 and over			
	No.	%	No.	%	No.	%	No.	%
P & P†	21	18	10	6	5	2	36	6
IA	5	4	6	4	4	1	15	3
IB	48	42	28	17	16	5	92	16
IC	2	2	6	4	5	2	13	2
IIB	15	13	23	14	43	14	81	14
IIC	17	15	44	27	87	29	148	25
IIIC	6	5	28	17	101	33	135	24
Worse	1	1	16	11	43	14	60	10
Total	115	100	161	100	304	100	580	100

* 1940 Classification of the New York Heart Association.

† Possible and potential heart disease.

I. Functional Classification (degree of cardiac disability)
- Class I. Ordinary physical activity does not cause discomfort
- Class II. Ordinary physical activity causes slight discomfort
- Class III. Ordinary physical activity causes marked discomfort
- Class IV. Unable to carry on any physical activity without discomfort

II. Therapeutic Classification (recommendations for physical activity)
- Class A. Physical activity need not be restricted
- Class B. Ordinary physical activity need not be restricted, but should be advised against unusually severe or competitive efforts.
- Class C. Ordinary physical activity should be moderately restricted and more strenuous habitual efforts should be discontinued.
- Class D. Ordinary physical activity should be markedly restricted
- Class E. Should be at complete rest, confined to bed or chair.

Work Status

It might be anticipated that the highest proportion of employment would be found among those patients having the most favorable functional and therapeutic classification. This was generally true with the exception that those diagnosed as having possible and potential heart disease showed a slightly lower percentage of employment than those in functional class I. Of particular interest is the substantial numbers in functional class III and therapeutic classes C, D, and E who were found in full time or limited employment. The figures are given in table 4.

TABLE 4.—*Functional and Therapeutic Classification* and Working Status of 580 Patients with Heart Disease*

Functional & Therapeutic Classification	Percentage Distribution				Total
	Working		Not working		
	Full-time	Limited†	Cardiac Reason	Other Reason‡	
	%	%	%	%	%
P & P§	83	2	2	13	100
IA	93	7	0	0	100
IB	83	6	0	11	100
IC	78	0	7	15	100
IIB	65	14	9	12	100
IIC	57	13	21	9	100
IIIC	23	27	42	8	100
Worse than IIIC	16	28	56	0	100

* 1940 Classification of the New York Heart Association (See table 3).

† Limited as to hours per day, hours per week and taxing features.

‡ Includes unemployed, and illness or disability other than cardiac.

§ Possible and potential heart disease.

An analysis of the relationship between age and sex and occupational status showed that for all categories employment was more frequent in the younger age groups. The details of this analysis are shown in table 5. It is interesting to note that the older patients more frequently attributed unemployment to cardiac causes than did the younger groups although in all probability age itself was the major factor in many cases. Table 5 also shows that a higher proportion of females than of males were working, a fact which can be attributed to home-making activities of the former. That this may reasonably be considered an occupation has been brought out in a previous publication.[9]

Of the entire series of 580 patients, approximately 54 per cent or 312, were working full time and approximately 16 per cent or 91 were doing limited work. Thus, 403 of the individuals in the series can be considered to have been working at the time the study was conducted. Table 6 shows, in broad occupational categories, the type of work done by those in the several etiologic classes of heart disease and table 7 shows the types of occupation found in the three age groups. The most frequent occupation is that of housewife, with "white collar" work and students second and unskilled labor third in frequency for those doing full time work. Among those having the less favorable functional and therapeutic classifications (IIIC or worse) housework and unskilled labor are the leading pursuits (table 8), a finding which is undoubtedly influenced to a considerable degree by the nature of the population from which the clinic draws its patients. Since these occupations are likely to entail strenuous physical exertion, an attempt was made to evaluate the taxing features in each case.

TABLE 5.—*Work Status of 580 Patients with Heart Disease According to Age and Sex*

Work Status	Percentage Distribution							
	Male				Female			
	0-34	35-54	55 and over	Total	0-34	35-54	55 and over	Total
	%	%	%	%	%	%	%	%
Full time work	80	59	30	45	90	70	45	64
Limited* work	0	9	10	8	2	21	40	25
Not working (cardiac)	6	22	48	35	2	7	11	7
Not working (other)†	14	10	12	12	6	2	4	4
Total	100	100	100	100	100	100	100	100

* Limited in respect to hours per day, hours per week, and taxing features.

† Includes unemployed and illness or disability other than cardiac.

The taxing features of a job are very difficult to evaluate. They include physical effort such as carrying, lifting, climbing, and pushing; long working hours and excessive traveling time;

tension, responsibility and other emotional factors. In most instances the patient's evaluation of a taxing feature must be accepted. For one particular IIB patient, carrying loads, standing or climbing stairs may not appear excessive, while for another IIB patient the same amount of work may be very strenuous.

In this study each patient was asked about specific features of his job and whether he considered them taxing. On the basis of this purely subjective evaluation, an attempt was made to ascertain the proportion of cardiac patients who had taxing jobs (table 9). Forty-two per cent had jobs without any taxing features. How this proportion would compare with a sample of a normal population cannot be stated, but presumably it is more important for an individual with heart disease than for a normal person to be spared any avoidable occupational stress. Apparently this was not the case for a majority of the patients in this series, although in general a smaller proportion of patients with a poor functional and therapeutic classification were in occupations with taxing features than those cardiacs whose activity was less restricted.

TABLE 6.—*Etiology and Occupation* of 403 Patients with Heart Disease Who Were Working in 1949*

Etiology	Percentage Distribution													
	Full Time Work (312 Patients)							Limited Work (91 Patients)						
	Occupation						Total	Occupation						Total
	0	I	II	IV	V	VI		0	I	II	IV	V	VI	
Rheumatic	1	29	39	7	11	13	100	0	4	82	0	0	14	100
Degenerative†	4	19	41	12	5	19	100	3	3	64	16	3	11	100
Other and unknown‡	2	18	36	0	4	40	100	17	0	66	0	0	17	100
All Types	3	24	39	8	7	19	100	3	3	68	11	2	13	100

* Occupational Classification of War Manpower Commission
O—professional or self employed
I—student, clerical, salesman
II—own housework
IV—skilled
V—semiskilled
VI—unskilled and domestic not self employed

† Includes hypertensive heart disease, hypertensive and arteriosclerotic heart disease, and arteriosclerotic heart disease.

‡ Includes congenital heart disease, syphilitic heart disease, cor pulmonale and etiology unknown.

TABLE 7.—*Age and Occupation* of 403 Patients with Heart Disease Working in 1949*

Age	Percentage Distribution													
	Full-time Work (312 patients) Occupation							Limited Work (91 patients) Occupation						
	0	I	II	IV	V	VI	Total	0	I	II	IV	V	VI	Total
0–34	3	36	37	6	7	11	100	0	0	0	0	0	100	100
35–54	1	19	39	6	10	25	100	0	0	73	4	4	19	100
55 and over	4	16	42	11	5	22	100	5	3	69	14	1	8	100
All ages	3	23	39	8	7	20	100	3	2	70	11	2	12	100

* Occupational Code of War Manpower Commission (see table 6 for explanation).

TABLE 8.—*Occupation* and Functional and Therapeutic Classification of 403 Patients with Heart Disease Working in 1949*

Functional & Therapeutic Classification	Percentage Distribution						
	Full-time and Limited Work						Total
	0	I	II	IV	V	VI	
P & P & IA	0	33	29	11	11	16	100
IB	3	37	33	6	6	15	100
IC	0	40	40	10	10	0	100
IIB	2	6	55	8	8	22	100
IIC	2	14	46	11	6	21	100
IIIC	3	7	62	6	3	19	100
Worse	12	3	55	12	3	16	100

* Occupational Classification of War Manpower Commission (see table 6 for explanation).

TABLE 9.—*Taxing Features in the Occupations of 311 Patients Working Full Time*

Functional & Therapeutic Classification	Taxing Features Absent		Taxing Features Present	
	No.	%	No.	%
P & P	10	35	19	65
IA	6	46	7	54
IB	34	45	41	55
IC	5	50	5	50
IIB	15	28	39	72
IIC	41	50	47	50
IIIC	15	47	17	53
Worse	6	60	4	40
All Classes	132	42	179	58

Absenteeism

In analyzing the records for absenteeism, only those patients were included who were employed full time in jobs other than housework. There were 189 who fell in this category. Of this number, 159 lost no time from work during 1949 for cardiac reasons and 153 lost no time because of any illness. Sickness disability due to heart disease, when it occurred, lasted for more than 30 days in 11 instances and for longer than 60 days in 5 cases out of a total of 30 cases of cardiac disability. Noncardiac disabilities were generally of shorter duration, The details are given in table 10. If an average is calculated for the entire group, it is found that sickness absenteeism for all causes, cardiac and other, is approximately nine days per year, which, incidentally, is about the national average for all industrial workers.[10]

Table 10.—*Time Lost from Work in 1949 of 189 Patients with Heart Disease Working Full Time**

Age	Days Lost											
	Cardiac Reasons						Noncardiac Illness					
	No. Cases	Days Lost					No. Cases	Days Lost				
		0	1–6	7–29	30–59	60 and over		0	1–6	7–29	30–59	60 and over
0–34	61	56	3	2	0	0	60	46	5	8	0	1
35–54	65	56	1	4	3	1	65	52	4	6	3	0
55 and over	63	47	4	5	3	4	64	55	4	5	0	0
Total	189	159	8	11	6	5	189	153	13	19	3	1

* Exclusive of housework.

Summary

1. An analysis of the occupational status of 580 adult cardiac clinic patients in 1949 showed that 45 per cent of the males and 64 per cent of the females were doing full time work and that an additional 8 per cent of males and 25 per cent of females were doing limited work.

2. With increasing age, there is a decreasing likelihood of employment for cardiacs just as is the case for noncardiacs.

3. Paradoxically, older patients tend to attribute their unemployment to cardiac reasons more frequently than do younger patients, regardless of the functional and therapeutic classification.

4. The most common occupations in the group studied were housewife, "white collar" work (including students) and unskilled labor, an occupational grouping which is probably due, at least in part, to the population from which the clinic draws.

5. A majority of the employed persons felt that their jobs entailed one or more taxing features, suggesting a large field for the application of selective placement.

6. Of 189 patients employed full time in jobs other than housework, 159 lost no time from work in 1949 due to cardiac reasons, and 153 lost no time because of any illness. The average duration of sickness absenteeism among the group studied was no greater than that of the employed population in general.

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CLINICAL PROGRESS

Editor: HERRMAN L. BLUMGART, M.D.

Associate Editor: A. STONE FREEDBERG, M.D.

Renal Factor in Congestive Heart Failure

By EUGENE A. STEAD, JR., M.D.

PATIENTS with edema of congestive heart failure may be divided into two groups: (a) those with edema caused by an abnormal redistribution of the fluid normally present in the body, and (b) those with edema caused by an absolute increase in the amount of fluid present in the body. The patient with no previous history of dyspnea, who has sudden pulmonary edema caused by a massive myocardial infarct, belongs to the first group. Edema of the lungs develops suddenly without a change in body weight. The fluid collecting in the lungs comes from that originally present in the blood stream and from fluid pulled into the blood stream from the tissues. The second group is exemplified by the patient with slowly progressive generalized failure of the heart who over a period of weeks has gained 35 to 100 pounds. In this patient the fluid intake has exceeded the fluid output over a long period of time. In the last analysis, the fluid has been retained in the body because the kidneys have failed to excrete it. This retention of fluid by the kidney is the subject of our present discussion of the renal factor in congestive failure. In most patients with congestive failure both the abnormal distribution of fluid and the abnormal increase in weight from edema are present.

Observations of patients with heart failure who gain weight from edema show the following generally agreed upon findings: (1) The renal excretion of sodium chloride is markedly reduced. (2) The night volume of urine is increased and the day volume decreased. (3) The ability to excrete water at a maximal rate is impaired, but if salt is not given, the average patient in moderate congestive failure can excrete water sufficiently well to tolerate a fluid intake of several thousand cc. of water without difficulty. (4) The concentration of sodium and chloride in the blood is frequently moderately lowered. (5) The plasma volume is increased. (6) The venous pressure is raised.

An excess of Cl^- produced by the giving of an acidifying salt, as ammonium chloride, does not cause edema. During the excretion of the excess Cl^-, a variable amount of Na^+ and water is lost. It is generally stated that Na^+ causes retention of fluid. In most instances the Cl^- has been available in the diet and the effects of giving excess Na^+ with rigid restriction of Cl^- has rarely been tried. Potassium does not lead to water retention.

An understanding of the mechanisms causing retention of sodium chloride and water in heart failure has been hampered by the lack of knowledge of factors controlling excretion of sodium chloride and water in normal subjects. This problem is now being studied extensively in many laboratories.

In normal man, increases and decreases in water excretion are controlled by changes in the amount of water reabsorbed by the tubules and not by changes in renal blood flow and glomerular filtration. The posterior lobe of the pituitary gland produces an antidiuretic hormone (ADH) which causes marked oliguria by increasing the tubular reabsorption of water. The secretion of ADH is inhibited by lowering of the total osmotic pressure of the plasma (not colloid osmotic pressure). The secretion of

ADH is caused by a rise in osmotic pressure or by many emotional, neurogenic, and pharmacologic stimuli. The osmoreceptors which respond to changes in osmotic pressure are located in the area supplied by the internal carotid artery.

There is no clearcut evidence that variations in ADH secretion have any effect on Na^+ and Cl^- excretion in normal man. Injections of minute quantities of Pitressin produce the same changes in urine volume and sodium chloride concentration as does the production of endogenous Pitressin by the administration of 0.9 per cent sodium chloride solution intravenously. ADH does cause an increase in urine concentration but the product of urine volume and salt concentration is unchanged. When concentrated sodium chloride solutions are given intravenously, a large output of water results which cannot be stopped by the injection of Pitressin. Thus, water excretion can be increased by mechanisms which cause increased sodium chloride excretion, but sodium chloride excretion is not changed by varying the water output by the injection of Pitressin.

These observations on normal subjects have led most observers to believe that posterior pituitary ADH is not of primary importance in the edema of congestive failure and that its presence in the urine in patients with congestive heart failure represents an effect on the osmoreceptors secondary to the retention of salt. The finding of a tendency towards reduced concentration of sodium and chloride in the serum of patients with congestive failure raises the question of the stimulus for the production of ADH in the presence of a decreased concentration of electrolytes, as this condition normally inhibits ADH production. It is possible that the "set" of the osmoreceptors may change in many illnesses and that in chronic heart failure a moderate reduction of electrolyte concentration will no longer stimulate the osmoreceptors. Other antidiuretic hormones may be present and important in congestive failure. It is also possible that the action of posterior pituitary ADH in patients with congestive heart failure differs from that in normal subjects.

The excretion of Na^+ and Cl^- in alkalosis and acidosis has been studied rather extensively. This does not seem to be the real crux of the problem in congestive heart failure. In the latter both Na^+ and Cl^- are retained, and our problem is what controls the excretion of the balanced mixture rather than the excess of either Na^+ or Cl^-.

A decrease in the excretion of Na^+ and Cl^- occurs in normal subjects during exercise, sitting, motionless standing, and sleep. When sodium chloride is restricted in the diet, the extracellular fluid volume decreases and the excretion of sodium chloride in the urine decreases. When the intake of sodium chloride is increased, the extracellular space expands and the excretion of sodium chloride in the urine rises. Retention of salt occurs at various times during the menstrual cycle. The administration of large quantities of testosterone, adrenocorticotropic hormone (ACTH) and cortisone usually causes retention of sodium chloride. The available data indicate that these variations in excretion are produced by changing the amount of sodium chloride reabsorbed by the tubules and not by changing the renal blood flow and glomerular filtration rate. In this respect, the control of excretion of sodium chloride seems to parallel the mechanism for the control of the excretion of water. The sodium chloride control differs in that it is much more sluggish and the factors acting on the tubules to increase and decrease the excretion of sodium chloride have not been defined. It is known that ACTH in large doses will usually cause initial retention of sodium. Whether ACTH in physiologic doses causes similar sodium retention remains to be determined. It is likely that the degree of salt loading and salt depletion will influence the action of the hormone. Whether the normal hourly variations in sodium chloride excretion are caused by the action of various hormones on the kidney tubules, by changes in filtration rate, by changes produced directly in the kidney, by changes in the electrolyte composition of the blood circulating through them, or by some other mechanism remains to be determined.

Sodium chloride retention is a characteristic finding in chronic congestive heart failure. The inability to excrete salt is relative rather than

absolute. The patient with heart failure varies his sodium chloride excretion as does a normal subject with exercise, infection, trauma. The abnormal change is quantitative rather than qualitative. The cardiac patient under a given stimulus for salt retention merely retains more than the normal amount of salt and under conditions where the normal person loses salt rapidly, the patient with chronic failure loses it slowly. The patient with heart failure does show one qualitative peculiarity. He excretes more salt during the night than during the day. This may be an expression of the fact that his circulation becomes increasingly abnormal with exercise and tends to become more normal during rest.

There are several possible explanations for the slow excretion of sodium chloride in patients with heart failure. Many persons believe that the backing up of blood behind the failing ventricles causes an increase in venous pressure in the systemic venous system. This in turn causes a rise in capillary pressure and water is forced out into the tissues. Salt and water taken in the diet then pass through the blood stream to the tissues and are not excreted by the kidneys because of the prerenal deviation of water and salt. This thesis seems unlikely because the plasma volume in chronic congestive failure is increased rather than decreased and because the quantitative difficulties in handling sodium chloride persist after the venous pressure has been returned to normal by the use of salt restriction and mercurial diuretics. This explanation also fails to account for the similar retention of salt which occurs after hemorrhage or trauma.

Other investigators have felt that the impairment of sodium chloride excretion results from the high venous pressure in the kidneys produced by backward failure. It has been shown in animal experiments that a rise in venous pressure will cause a decrease in sodium chloride output without a change in renal blood flow or filtration rate. Whether this change occurs in man and whether it is of the order of magnitude seen in congestive failure and whether this stimulus for sodium retention remains effective for the weeks and years which a patient may stay in failure are problems for the experimental laboratory. The observation that in man the abnormal sodium chloride retention persists after the central venous pressure returns to normal remains to be explained. This thesis will not explain similar retention of sodium chloride after hemorrhage.

Some investigators have believed that the primary cause for salt retention in congestive failure is the increased avidity of the renal tubules for salt because of hormonal stimulation. They point out that ACTH, cortisone, and testosterone cause salt retention in normal subjects. An insufficient circulation is certainly a stress and would be expected to stimulate the pituitary-adrenal mechanism. Increased urinary corticoid excretion has been reported in chronic failure, and studies of sweat secretion are compatible with increased adrenal cortical function. One would expect to find comparable retention of sodium chloride when the circulation is decreased by hemorrhage. The weakness of this argument lies purely in its quantitative aspects. Patients with heart failure show the same qualitative changes to stress, exercise, and anoxia as normal subjects. It remains to be shown that the body produces sufficient salt-retaining hormones to cause the massive edema of chronic heart failure. Either some other factors are operative or, in comparison to other stresses, the stress of congestive failure produces unusually large amounts of salt-retaining hormones.

There is a marked disturbance in renal hemodynamics in patients with chronic heart failure. In subjects who form edema at rest on an unrestricted diet, the findings are surprisingly uniform. The renal blood flow is greatly reduced and the amount of glomerular filtrate is decreased. The amount of filtrate obtained from each unit of plasma flowing through the glomeruli is, however, greatly increased. The fall in filtration rate causes a decrease in the amount of sodium chloride presented to the tubules. The tubules reabsorb nearly all of the filtered sodium chloride, but the absolute amount of sodium chloride filtered is so small that the absolute amount of sodium chloride reabsorbed is much less than in the normal subject. This remains true if 100 per cent of the filtered sodium chloride is reabsorbed. In

chronic failure, the per cent of filtered sodium chloride which is reabsorbed is increased, but the absolute amount compared to that reabsorbed by a normal subject is decreased. The disturbed renal hemodynamics of chronic failure are not correlated with changes in venous pressure, but they do correlate with the reduced cardiac output of chronic failure.

Some investigators, including the author, have believed that this reduction in filtered sodium chloride was the primary factor in causing the edema of chronic heart failure. They have reasoned that the renal tubules normally have as one of their main functions the retention of these ions and that the tubules cannot avoid reabsorbing nearly all the sodium chloride when the amount presented to them becomes very small. Attention is called to the interesting fact that tubular function remains surprisingly good in congestive failure and that there is only a moderate reduction in renal oxygen consumption. Comparable decrease in filtration rate in glomerular nephritis or vascular disease of the kidney results in much lower rates of oxygen consumption than is seen in congestive failure. This thesis states that there is a normal balance between filtered sodium and tubular reabsorptive function and that when glomerular filtration is lowered without a corresponding decrease in tubular function, edema occurs; if glomerular filtration is lowered with a corresponding decrease in tubular function because of disease of the tubules, the tendency to edema is decreased.

Many objections have been raised to the glomerular-tubular imbalance concept of sodium retention. In normal subjects, the variations in sodium excretion are controlled to a greater degree by changing tubular function than by changing filtration rate. Likewise, in patients with chronic failure, changes in sodium excretion can be produced which seem to be related to changes in tubular function. The proponents of the glomerular-tubular imbalance hypothesis answer that the directional changes produced in normal subjects are also produced in patients with cardiac failure, but that the extent of the change is governed to a large degree by the amount of sodium filtered. For example, light exercise, which in a normal subject causes only slight retention of salt and water, will produce massive edema in the patient with heart failure.

Various investigators have pointed out that edema may disappear without demonstrable change in filtration rate. Again it should be emphasized that there are many situations which influence sodium excretion. Massive edema from heart failure rarely persists at bed rest unless the filtration rate is markedly reduced. On the other hand, on a sodium restricted diet, edema may disappear even though the filtration rate remains low.

The fact that reduced glomerular filtration in other diseases, as chronic glomerular nephritis and marked nephrosclerosis, does not cause the same tendency to edema so characteristic of patients with congestive failure has been given as an objection to the glomerulotubular imbalance hypothesis. This observation actually supports the hypothesis because, in these diseases, tubular destruction is going along with glomerular destruction and the reduced filtration is balanced by the decrease in tubular function.

In summary, there is still no general agreement on the relative importance of the mechanisms by which salt and water are retained in chronic heart failure. In recent years more emphasis has been placed on determining the role of the kidney in controlling salt and water metabolism and less attention has been paid to mechanical factors diverting salt and water from the blood stream to the tissues. The student of heart failure has become interested in the means by which a reduced cardiac output and elevated venous pressure affect renal function. He has been pulled into the fields of endocrinology to evaluate the effect of the stress of reduced circulation and decreased venous oxygen tension on the pituitary-adrenal relationship and on other aspects of metabolism. He has had to observe the effects of diets restricted in protein and salt on the function of the pituitary, adrenal, and thyroid glands and to consider the effects of chronic illness on the electrolyte composition of cells. Problems in physical chemistry loom large as one tries to define the mechanisms by which osmoreceptors operate and attempts to evaluate the scattered

evidence that the "osmotic set" of these receptors may vary. The means by which the body regulates the concentration of electrolytes and the amount of extracellular and intracellular fluids remain problems for the future.

Once the salt and water are present in the body there is general agreement that the distribution of the retained water is largely determined by local factors. The greatest swelling occurs where the capillary pressure is the highest, the tissue pressure the lowest, and the lymphatic flow least. When a normal subject lying in the recumbent position is given physiologic saline solution at a faster rate than his kidney can excrete the fluid, he gains weight. As there are no areas of abnormally high capillary pressure, the fluid accumulates in areas where a considerable increase in volume can occur with a minimum rise in tissue pressure. The edema first becomes visible in the soft tissues about the eyes. If the subject now stands erect, he will have a high capillary pressure in the portion of the body below heart level. Fluid will now be deposited in the lower part of the body. In either position there will be no tendency for fluid to accumulate in the lungs.

The situation is entirely different when fluid is given intravenously to a patient with left ventricular failure. The high capillary pressure in the lungs causes an unusual portion of the fluid given to accumulate in the lungs, and frank pulmonary edema may be precipitated with a minimal increase in body weight. If during the course of heart disease the right ventricle is weakened to the same degree as the left, one loses this marked predisposition for pulmonary edema, and the patient gains large amounts of weight without drowning.

The treatment of edema of congestive heart failure can be divided into two phases: (1) Measures which make the circulation adequate for the needs of the body. When these measures are effective, edema will not develop on a normal diet. (2) Measures for preventing edema when the circulation remains inadequate. If the circulation cannot be restored to a level adequate for the activity of the patient, edema will occur on an unrestricted diet.

(1) To make the circulation adequate for body needs

a. Increase the output of the heart and restore the circulation to a normal level. Digitalis is the only effective drug for this purpose.

b. Decrease activity of the body so that fewer liters of blood have to be pumped per day. This reduction in the requirements of the body for blood allows the damaged heart to supply normal quantities of blood to all vital organs. This is accomplished by weight reduction, limitations on stair climbing, and on work.

c. Correct any diseased states which increase the requirements of the body for blood. Anxiety, hyperthyroidism, anemia, beriberi, arteriovenous fistula, and patent ductus arteriosus all increase the output of a normal heart. Removing this extra load may make the output of the heart adequate for the needs of the body.

d. Correct any diseased states which have an adverse effect on myocardial function. Hypertension, pulmonary infections, pulmonary infarctions, asthma, anoxemia, and myxedema decrease the functional capacity of the heart.

(2) To prevent edema in the presence of an inadequate circulation.

a. Restriction of the sodium chloride in the diet. This is the most satisfactory measure with intelligent and cooperative persons. The restriction must be marked enough to produce the desired results. In many patients, the sodium intake must be reduced to 150 to 200 mg. per day. This means a marked reduction in protein intake unless the diet is supplemented with special protein preparations low in sodium, such as dialyzed milk. Many physicians have felt that the restriction in protein intake was undesirable and have devised diets to supply approximately 1 Gm. of protein per Kg. Others have felt that the metabolic adjustment that the body makes to the low protein intake is desirable and has a favorable effect on the patient with chronic heart failure. This problem needs further investigation.

The diet should be controlled by following the excretion of Cl^- in the urine. For this reason salt substitutes are not desirable.

b. Increased excretion of sodium chloride by the use of diuretics. The mercurial diuretics are the most useful. (The intravenous route should be avoided.) They should be given sufficiently often to maintain the patient at a constant

weight. They must be used cautiously if the patient is on a restricted intake of sodium chloride. Ammonium chloride is useful in increasing the effectiveness of the mercurial diuretics.

c. Removal of the sodium from the gastrointestinal tract by the use of ion exchange resins. This method is still in the experimental stage.

d. Removal of fluid from the body by mechanical means. Thoracentesis and abdominal paracentesis may hasten convalescence. Large quantities of subcutaneous edema may be drained off by inserting several number 14 needles into the subcutaneous tissues above the ankles. After a few minutes the needles are removed and the fluid drains freely along the needle tract.

This discussion of congestive failure differs from that present in any standard text book of medicine of 10 years ago in four ways. (1) It is recognized that the reduction of sodium chloride to 2 Gm. per 24 hours is inadequate in many patients and that diets containing 200 mg. or less of sodium are practical. (2) The old Karell diet of 200 cc. of milk four times per day contains about 400 mg. of sodium and is not the best diet for the severest forms of congestive failure. (3) Treatment by sodium restriction is preferred to treatment by diuretics, and the dietary therapy is controlled by the measurement of the chloride output. (4) No mention is made of fluid restriction.

In the years of fluid restriction without salt restriction patients were miserable from thirst. It was gradually learned that the cardiac patient's difficulty was in the excretion of salt and that in the absence of salt he could tolerate a large amount of water. It also became obvious that the craving for water disappears as the salt intake is restricted. The amount of water needed by the patient with congestive heart failure varies greatly. If he is dehydrated, febrile, and in a hot environment, his water requirements may rise to between 3000 to 6000 cc. per 24 hours for a short period of time. If he is on a diet which contains a minimum of nitrogen and electrolytes, his water requirements will be reduced below that of a person on a normal diet.

The emphasis on low sodium diets in congestive heart failure has led to the occasional development of weakness and anuria from Na^+ depletion. This syndrome of Na^+ loss is not uncommonly seen in patients with renal disease who are placed on a rigidly restricted sodium intake, as the kidneys may have reduced ability to retain sodium because of disease of the renal tubules. It is rarely seen in congestive heart failure unless sodium restriction has been combined with the use of mercurial diuretic agents.

In severe failure the mercurial diuretic may cause a diuresis of salt with very little increase in the output of water. This leads to a lowering of the sodium and chloride concentrations in the blood. It is probable that shifts of sodium from extracellular fluids to cells occur in the severest forms of failure and that a low concentration of Na^+ does not necessarily mean excess loss through the urine. Finally, the "set" of the osmoreceptors regulating the output of the posterior pituitary ADH may be altered so that the body accepts a lowered level of electrolytes. The administration of sodium chloride in a 3 to 5 per cent solution may cause a dramatic improvement in some of these patients. In others it is without effect. In still others acute pulmonary edema may be precipitated.

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ABSTRACTS

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BACTERIAL ENDOCARDITIS

Glynn, L. E. and Reinhold, J. D. C.: The relationship of Idiopathic Cardiac Hypertrophy to Foetal Endocarditis. Arch. Dis. Childhood **25**: 170 (June), 1950.

The authors present a case of a 21 month old boy who died suddenly while in cardiac failure. The child was normal at birth. At autopsy the heart was enlarged with hypertrophy of both ventricles. The endocardium of both ventricles was markedly thickened and opaque. There was nodular thickening of both the mitral and tricuspid valves. On microscopic examination there was hypertrophy of the subendothelial trabeculae with elastosis of the endocardium. There was no evidence of inflammation except in the pericardium.

Fibroelastosis of the endocardium is not found in glycogenic cardiomegaly. However, it has been found in all of the nonglycogen group of idiopathic cardiac hypertrophy. The authors support the view that so called fetal endocarditis is not inflammatory in origin, but is due to impaired nutrition, secondary to interference by the thickened endocardium. In 70 per cent of the cases of so-called fetal endocarditis, fibroelastosis is seen and may, in those surviving the neonatal period, lead to idiopathic cardiac hypertrophy in children.

MARGOLIES

Gorlin, R., Favoner, C. B., and Emery, F. J.: Long Term Follow-up Study of Penicillin-Treated Subacute Bacterial Endocarditis. New England J. Med. **242**: 995 (June), 1950.

The purpose of this study was to show the altered clinical pattern and results of penicillin therapy in patients with subacute bacterial endocarditis. Thirty-eight cases were studied, all of whom received 200,000 units or more of penicillin for 10 days or longer. All were followed for one year or longer or until they came to autopsy.

The authors found that with penicillin therapy the death rate was markedly reduced. In this series, 70 per cent survived. Prognosis was poor in patients who developed congestive failure early in the disease, when sustained fever persisted for four days of penicillin therapy, and when a streptococcus skin test remained negative during therapy. The embolic phenomena and renal lesions were not as prominent as in the pre-penicillin era. Late complications were usually confined to recurrence of the bacterial endocarditis and congestive failure. The over-all picture showed that 75 per cent of patients who recovered from the bacterial endocarditis showed no permanent ill effects.

NADLER

Viciu, E. and Iliescu, M.: The Function of the Defense Mechanism of the Reticuloendothelial System in Endocarditis Lenta. Cardiologia **16**: 179, 1950.

Injection of an activator of the reticuloendothelial system (reticulin) produces no change of the alexin titer in active subacute bacterial endocarditis; inactive cases show an increase of the titer within 24 hours. This observation supports the view that subacute bacterial endocarditis is not primarily restricted to the endocardium but represents a general disease of the reticuloendothelial system

with exhaustion of its function to produce additional antibodies. This may explain the failure of certain cases to respond to antibiotic therapy. The alexin test with reticulin permits the determination of the defensive function of the organism and should be used routinely at the time of determination of penicillin sensitivity. Weakness of the reactivity of the body requires substitution therapy (adrenocortical hormone) in addition to treatment with antibiotics.

PICK

BLOOD COAGULATION

Wassersug, J. D.: Use of Human Thrombin in Some Cases of Pulmonary Hemorrhage. Dis. of Chest **17**: 354 (March), 1950.

Five patients with active tuberculosis who showed persistent blood streaking in the sputum were treated with human thrombin administered by aerosol, using oxygen. One course of treatment appeared to provide all the patients with relief lasting for at least as long as two weeks. The therapy, however, did not preclude the resumption of bleeding. No sensitizing action of the thrombin was noted on subsequent administrations.

ABRAMSON

Wheatley, D.: Chilblains and Prothrombin Levels. Lancet **2**: 712 (April), 1950.

On the supposition that in chilblains there is a diminished blood coagulation as well as a defective peripheral circulation and increased capillary permeability, the author gave vitamin K to 26 patients suffering from this condition, despite the fact that the prothrombin level was generally normal in the group. Clinically 23 cases responded completely to vitamin K and 3 failed to show any improvement. The basis for such a therapeutic effect could not be substantiated by any experimental evidence.

ABRAMSON

Lasser, R. P., Versakos, M., and Loewe, L.: The Influence of Aureomycin on Human Coagulability. Angiology **1**: 233 (June), 1950.

Thirteen patients received 500 mg. of aureomycin every six hours for periods varying from 12 hours to 10 days. Lee-White coagulation times, in vitro heparin tolerance tests, and aureomycin blood levels were determined in all patients. Prothrombin times, whole and dilute, and fibrinogen B levels were determined in 8 patients. No significant effect on coagulation was observed.

WESSLER

Alexander, B., Goldstein, R. and Landwehr, G.: The Prothrombin Conversion Accelerator of Serum (SPCA): Its Partial Purification and Its Properties Compared with Serum Ac-Globulin. J. Clin. Investigation **29**: 881 (July), 1950.

The authors report the isolation and partial purification of a serum prothrombin conversion accelerator (SPCA) which, in the presence of a labile plasma component, accelerates the conversion of prothrombin to thrombin. Certain differences between this substance and serum Ac-globulin may be explained by the hypothesis that serum Ac-globulin is a combination of SPCA and *plasma* Ac-globulin. Purified SPCA accelerated the coagulation of hemophilic blood, heparinized, and silicon blood. This substance may be identical with thrombokinase. Human serum contains less than 3 mg. of SPCA per 100 ml.

WAIFE

Wier, R. H., Eagen, J. C., and Wolfson, S. A.: The Effect of Dicumarol on the Erythrocyte Sedimentation Rate. Ann. Int. Med. **33**: 354 (July), 1950.

On the basis of observations in 19 patients with and without myocardial infarction, the authors conclude that therapeutically optimal reductions in the blood prothrombin level, induced by dicumarol administration in the usual dosage, do not significantly influence the erythrocyte sedimentation rate. Any acceleration of the sedimentation rate which occurred in these patients could be related to the pathologic process itself and was not affected by the lowered prothrombin levels.

WENDKOS

CONGENITAL ANOMALIES

Taylor, B. E., Pollack, A. A., Burchell, H. B., Clagett, O. T., Wood, E. H.: Studies of the Pulmonary and Systemic Arterial Pressure in Cases of Patent Ductus Arteriosus with Special Reference to Effects of Surgical Closure. J. Clin. Investigation **29**: 745 (June), 1950.

The average blood flow through a patent ductus arteriosus was found to be 7.4 (1.6 to 17.7) liters per minute for 6 patients in whom preoperative cardiac catheterization studies were performed. Calculations showed that 44 (23 to 80) per cent of the left ventricular output passed through the patent ductus. The outside diameter of the ductus, in 9 of 12 subjects on whom such studies were performed, averaged 9.9 mm. The average pulmonary arterial pressure was slightly above normal values. Closure of the patent ductus arteriosus in 15 patients produced an immediate slight increase in systemic systolic and diastolic arterial pressure. The pulmonary arterial pressure immediately decreased.

WAIFE

Healey, R. F., Dexter, L., Elkin, M., and Sosman, M. C.: Roentgenographic Changes in Pulmonic Stenosis. Am. J. Roentgenol. **63**: 813 (June), 1950

The most significant roentgenographic finding in 5 of 8 cases of isolated pulmonic valvular stenosis, and in another with a small right to left shunt, was a poststenotic dilatation of the main pulmonary artery which did not include the hilar or intrapul-

monary branches. Seven out of 9 cases failed to show cardiac or selective chamber enlargement. Left auricular enlargement was not observed in any case. The diagnosis of pulmonic stenosis was established by the demonstration of a higher systolic pressure in the right ventricle than in the pulmonary artery. Physiologically significant septal defects were excluded by a comparison of blood samples from the pulmonary artery, right heart chambers, superior vena cava and a systemic artery.

SCHWEDEL

Donzelot, E., Emam Zade, A. M., Heim de Balsac, R. and Collado Madera, S.: A Study of 25 Cases of Persistence of the Arterial Canal (Isolated and Complicated). Acta cardiol. **5**: 225, 1950.

The authors present a clinical and radiologic study of 25 cases of patent ductus arteriosus found among 314 instances of congenital heart disease. In the majority (85 per cent) of the observations, the presence of cyanosis indicated an association of this anomaly with other malformations of the heart. A continuous murmur of high localization was found in 17 cases. In 6 instances it was present, but atypical, and in 2 cases proved at autopsy, it was absent.

The authors discuss the symptomatology and the diagnostic problems of each particular case and the methods of diagnosis. As in other instances of congenital heart disease, the diagnosis of a patent ductus may be missed in about 20 per cent of cases.

PICK

CONGESTIVE HEART FAILURE

White, A. G., and Sachs, B. A.: Studies in Edema: Cholesterol and Its Relation to Protein Nitrogen in Edema Fluid. Science **112**: 18 (July), 1950.

The authors found that the cholesterol content of edema fluid from patients with congestive heart failure averaged 14.6 mg. per cent, and from patients with venous obstruction, 17.3 mg. per cent. This is in sharp contrast to the value found in patients with lymphatic obstruction, an average of 175.2 mg. per cent. This may serve to differentiate these types of edema. The total cholesterol was found to be related to the protein nitrogen content of the edema fluid.

SACHS

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Raab, W.: Clinical Course of Two Hundred Cases of Angina Pectoris Treated with Roentgen Irradiation of the Adrenals (1937–1947). Am. J. Roentgenol. **63**: 895 (June), 1950.

The author supervised the treatment of 200 patients with angina pectoris subjected to roentgen irradiation of their adrenal regions; 57 of these also received roentgen therapy of their upper dorsal and cervical spines for their "sympatheticoganglionitis." Treatment was based on the premise that angina is due to increased irritability of the adrenal medulla, leading to increased adrenaline excretion and sympathin formation and resulting in heart muscle anoxia, and to an inhibition of coronary arterial dilatation. The author claims that 76 per cent of all cases showed some improvement for an average period of 31 months. Ten per cent had relapses requiring repetition of therapy. Cases of angina of long standing and those with angina decubitus (presumably angina occurring without evident effort, which occurred in 49 per cent of the series) seemed more likely to fail to respond. No claim is made for a general life prolonging effect of roentgentherapy in these cases.

SCHWEDEL

Armbrust, C. A., Jr., and Levine, S. A.: The Treatment of Angina Pectoris with a Preparation of Khellin (Ammi Visnaga). Am. J. M. Sc. **220**: 127 (August), 1950.

Visammin (khellin) is one of the three active crystalline substances that has been isolated from the fruit of Ammi visnaga, a plant which grows wild in the eastern Mediterranean countries. The authors administered this substance (40 mg. three times daily by mouth) to 53 ambulatory patients with angina pectoris. Placebos identical in appearance were used during control periods. About 60 per cent of the cases used fewer nitroglycerine tablets, had fewer and milder attacks of pain and could walk greater distances while taking the visammin. Uncomfortable side effects, nausea, anorexia and dizziness occurred in about 60 per cent of the patients, and in many instances constituted a real deterrent to the use of the drug.

DURANT

Wolman, M.: Hypertrophy of the Branches of the Pulmonary Artery, and Its Possible Relationship with the So-Called Primary Pulmonary Arteriosclerosis in 2 Infants with Hypertrophy of the Right Heart. Am. J. M. Sc. **220**: 133 (August), 1950.

Two cases of so-called congenital "idiopathic" hypertrophy of the right heart are described, in each of which there was found a significant hypertrophic change of the pulmonary arteries. The opinion is expressed that the latter changes constitute the anatomic background or the first step toward primary pulmonary sclerosis, believed to be due in some cases to the described congenital malformation. It is further thought that congenital hypertrophy of the small pulmonary arteries might be the cause of the right heart hypertrophy.

DURANT

ELECTROCARDIOGRAPHY

Donzelot, E., Metianu, C., Durand, M., and Vlad, P.: The Mean Electrical Axis of QRS in the Last Sextant (From −150 to −90 Degrees) in Con-

genital Cardiacs. (Study of 30 Cases.) Arch. d. mal. du coeur **43:** 203 (March), 1950.

Deviation of the QRS axis in the direction given in the title was found in 30 instances (4.6 per cent) among tracings obtained from 650 patients with heart malformations. The diagnosis in 16 patients was tetralogy of Fallot. Twenty-nine subjects exhibited cyanosis. The patients ranged from 6 months to 24 years of age. The P axis lay between 0 and +90, that of T between −10 and +90 degrees. The duration of QRS was normal in 26, and prolonged (0.06 to 0.12 second) in 4 instances. The onset of the intrinsicoid deflection was delayed in lead V_1 in 10 instances, and in lead V_6 in 1 instance out of 13 precordial tracings. The precordial leads displayed high voltage of QRS, mainly in leads V_1 and V_2. R was almost invariably high on the right side of the precordium, followed by a depressed and upward convex S-T segment and an inverted or diphasic −+ T wave. In lead V_6, the QRS complex most often showed the rS type.

Only two patients were in heart failure. In 27 instances, radiologic examination disclosed a heart enlargement usually produced by right ventricular hypertrophy. In 2 cases (Fallot's tetralogy and complete transposition of great vessels with pulmonary stenosis and ventricular septal defect) autopsy showed enlargement of the right atrium and marked hypertrophy, accompanied by slight dilatation of the right ventricle with the apex formed chiefly by this ventricle.

BRUMLIK

Jouve, A., Buisson, P., Albouy, M., Velasque, P., and Bergier, G.: The Point of Origin of the Vectorcardiographic Loop. Its Determination. Its Practical Importance. Arch. d. mal. du coeur **43:** 215 (March), 1950.

The authors point out that sometimes it is not possible to construct the spatial vectorcardiogram from frontal and horizontal vectorial triangles because of their dissimilarity. The point of origin of the vectorcardiographic loop, i.e., the electric center or zero point, should, therefore, be determined as precisely as possible. This can be achieved on the basis of two assumptions: (1) the tracings obtained from the surface of the body at both ends of a straight line passing through the zero point are mirror images of each other, and (2) in all leads where axes are parallel the tracings have the same shape; in other words, their R/S ratios are equal. In practice, the zero point can be determined in the following way: lead I is taken as reference; in the left middle axillary line, a point is sought which yields a unipolar electrocardiogram resembling lead I in all details. The horizontal plane passing through this point also passes through the zero point. A unipolar electrocardiogram taken from a point in the right axilla, diametrically opposite to the one on the left, should be a mirror imagine of this lead, though of smaller amplitude. The level so defined is the correct level for taking horizontal vectorcardiograms. Its use eliminates the discrepancies formerly encountered. The same level should also be used for taking unipolar precordial leads. In doing so one will avoid the distortion of QRS and T in precordial electrocardiograms encountered in about 30 per cent of tracings taken in points V_1 to V_6 as recommended by the American-British Committee.

BRUMLIK

Dailheu-Geoffroy, P., and Merlen, J. F.: The Ventricular Gradient in Chronic Arterial Hypertension. Arch. d. mal. du coeur **43:** 363 (April), 1950.

The frontal plane projection of the ventricular gradient remained within normal limits in 86 per cent of 119 cases of essential hypertension. No attempt was made to correlate the changes with the clinical state, but it is pointed out that these observations argue against the presence of serious metabolic disturbances in myocardial function in subjects with slowly developing hypertension.

HECHT

Guyot, R., and Blum, J.: Premature Ventricular Escapes following Extrasystoles. Arch. d. mal. du coeur **43:** 459 (May), 1950.

The authors present the electrocardiographic observation of ventricular premature beats with varying and alternating contour giving rise to intermittent bigeminal rhythm. Escapes appearing in the long postextrasystolic intervals and interfering with the sinus impulses led to temporary disappearance of the sinus P waves from the tracing. The authors assume the presence of a hyperexcitable ventricular focus, the appearance of which in the electrocardiogram was enhanced by ventricular recovery during the long postextrasystolic interval.

PICK

Dailheu-Geoffroy, P.: Concerning the Distinction of Bundle Branch Blocks. Arch. d. mal. du coeur **43:** 422 (May), 1950.

The QRS complex in any pattern of bundle branch block can be divided into two parts: a smooth and narrow R wave and a slurred and broad S wave. The latter represents the electrocardiographic expression of the abnormal impulse propagation through the myocardium and is termed by the author " S wave " regardless of its positive or negative direction. A determination of the axis of the S wave permits localization of a bundle branch block lesion from the three standard leads. In 34 electrocardiograms representing various patterns of atypical bundle branch block, it could be demonstrated that the S axes invariably pointed from left to right in the presence of right bundle branch block and from right to left in the presence of left bundle branch block. The direction of the R axis, which determines the pattern of bundle branch block in the

standard leads, was found to be variable depending on the position of the heart and the degree of hypertrophy of the ventricles.

PICK

Tourniaire, A., Blum, J., Guyot, R., and Dumas, J. P.: A Critical Study of $T_1 < T_3$ and of Alterations of the Ventricular Complex in CF Leads in Vertical Hearts. Arch. d. mal. du coeur **43**: 434 (May), 1950.

The authors present six examples of the following electrocardiographic pattern: $T_1 < T_3$, P_2 and $P_3 > P_1$, the QRS axis between + 70 and + 80 degrees and inversion of QRS and T in CF precordial leads. Unipolar limb leads revealed vertical position of the heart and unipolar (V) chest leads showed no abnormalities. This syndrome, described previously as a coronary pattern, is found frequently in vertical hearts, especially in association with emphysema, and has no pathologic significance.

PICK

Malinow, M. R., and Langendorf, R.: Twenty Year Follow-up in a Case of Wolff-Parkinson-White Syndrome. Ann. Int. Med. **33**: 227 (July), 1950.

A healthy 24 year old man was first seen when he was 4½ years of age because of an acute respiratory infection and episodes of palpitation. The electrocardiogram revealed changes typical of anomalous atrioventricular excitation. During World War II, he served as a bomber pilot for three years without developing any cardiac symptoms. In 1946 a follow-up examination was made and electrocardiograms showed the persistence of the pattern of a short P-R interval and prolonged QRS complex. The contour was similar to that in the electrocardiograms taken when he was a child. An exercise test was performed, but no changes in the electrocardiographic contour occurred. Quinidine sulfate in the dosage of 0.8 Gm. given orally did not alter the electrocardiograms within two hours following administration.

WENDKOS

Uhley, M. H.: The Electrocardiogram in Congenital Heart Disease (a Postmortem Correlation Study of 53 Cases). Ann. Int. Med. **33**: 188 (July), 1950.

Congenital lesions can be divided into two groups by the electrocardiographic patterns they produce: specific and nonspecific. Both are pathognomonic for the existence of congenital heart disease in infancy and early childhood. The former indicate particular lesions, the latter the presence of congenital anomalies, the nature of which is indeterminate from the electrocardiogram alone. This classification decreases greatly in value beyond the period of infancy and childhood.

The specific patterns include the classical total inversion of all the components in lead I resulting from dextrocardia; the pattern of anterior wall coronary insufficiency or myocardial infarction in infancy resulting from an anomalous origin of the left coronary artery from the pulmonary artery; the pattern of combined heart strain resulting from congenital idiopathic hypertrophy: the pattern of left heart strain resulting from (a) lesions affecting the systemic outflow tract and aorta, (b) tricuspid atresia, (c) truncus arteriosus communis, and (d) a single ventricle. A congenital lesion of a nonspecific pattern can be suspected when there is electrocardiographic evidence of right heart strain or when two or three of the standard limb leads show large diphasic QRS complexes.

WENDKOS

di Guiseppe, Fr.: Contribution to the Picture of Post-Tachycardia Electrocardiographic Syndrome. Report of a Case. Acta cardiol. **5**: 174, 1950.

The author describes a case of supraventricular paroxysmal tachycardia which lasted 10 days. The attack was stopped by quinidine and was followed by a characteristic post-tachycardia electrocardiographic syndrome. The author thinks that such a syndrome results from the subepicardial ischemia of the myocardium.

AUTHOR

HYPERTENSION

Rau, G. C.: Experimental Hypertension Produced by a Plastic Capsule Applied to the Kidney. Science **111**: 229 (March) 1950.

A plastic capsule can be produced around the kidneys of experimental animals by spraying the kidneys with a butyl methacrylate polymer dissolved in acetone. The plastic solution hardens quickly into a capsule which is not disturbed by body fluids, temperature or movement. The rise in blood pressure was similar to that following cellophane applications to be kidneys.

WAIFE

Assali, N. S., and Prystowsky, H.: Effect of Adrenergic Blockade with a Benzodioxane Derivative, 933 F. on Hypertension of Toxemia of Pregnancy. Surg., Gynec. & Obst. **90**: 655 (June), 1950.

Using 933 F, an adrenergic blocking agent, the authors investigated the possible role of circulating sympathomimetic agents, such as epinephrine, in the genesis of toxemic hypertension. The study was performed on 5 patients with either severe pre-eclampsia or convulsive eclampsia. Benzodioxane produced very little or no fall in blood pressure in this group. It was therefore concluded that circulating epinephrine plays no role in the maintenance of the blood pressure in toxemic hypertension.

ABRAMSON

Weston, R. E., Hellman, L., Escher, D. J. W., Edelman, I. S., Grossman, J., and Leiter, L.: Studies on the Influence of the Low Sodium Cardiac Diet and the Kempner Regimen on Renal

Hemodynamics and Electrolyte Excretion in Hypertensive Subjects. J. Clin. Investigation **29**: 639 (June), 1950.

Renal hemodynamics and electrolyte metabolism were studied in 9 hypertensive patients without congestive heart failure. On a low salt cardiac diet (0.5 to 0.8 Gm. sodium) no conclusive changes in renal plasma flow, renal arteriolar resistance, plasma volume, maximal tubular capacity for *p*-aminohippurate excretion (Tm PAH) and in serum sodium and chloride occurred. However a decrease of 15 to 33 per cent in glomerular filtration rate (as measured by mannitol clearance) occurred in 5 of 6 patients. On the Kempner rice diet (less than 0.2 Gm. sodium), with additional use of mercurial diuretics in several patients, there was a significant decrease in glomerular filtration rate and a smaller decrease in renal plasma flow. In 7 subjects the renal afferent arteriolar resistance decreased, while in 5 patients the plasma volume fell.

In contrast to normal subjects, hypertensives showed a proportional relationship between urine volume and electrolyte excretion during water and mannitol diuresis. This may be the earliest sign of renal tubular damage in hypertension.

The authors suggest that there may be two possible dangers in a very low salt diet for hypertensives. In the presence of reduced renal function, a further fall in glomerular filtration rate may lead to serious azotemia, particularly if sodium loss is increased by mercurial diuretics. Furthermore, there may result a rapid loss of extracellular electrolyte in hypertensives with advanced renal disease. However, in most instances electrolyte loss and depressed renal function are not sufficiently serious to outweigh the therapeutic benefits of properly supervised dietary management.

WAIFE

Moss, W. G., and Wakerlin, G. E.: Role of the Nervous System in Experimental Renal Hypertension. Am. J. Physiol. **161**: 435 (June), 1950.

The authors found that the role of the nervous system in maintaining blood pressure levels in 65 renal hypertensive dogs did not differ from that in normotensive animals. Deep anesthesia produced identical pressure changes in hypertensive and nonhypertensive animals, and no difference in response occurred when adequate doses of autonomic blocking agents (dehydroergotamine, 883F, Dibenamine, tetraethylammonium chloride, and epidural procaine) were administered intravenously. There was a decrease in response to a cold pressor test (icepack on the abdomen for one minute) and to hyperventilation in early renal hypertensives, suggesting a decreased responsiveness of vascular centers. With this exception, which is temporary, it appears that the production of experimental renal hypertension in dogs does not bring about any permanent change in the tonic control of the blood vessels by the vasomotor center.

HECHT

Murphy, R. J. F.: The Effect of "Rice Diet" on Plasma Volume and Extracellular Fluid Space in Hypertensive Subject. J. Clin. Investigation **29**: 912 (July), 1950.

Data was obtained from 17 ambulatory patients (16 of whom were hypertensive) on the Kempner rice diet for a period of 100 days. Urine chloride excretion was used to check adherence to the diet. Significant decreases (about 10 per cent) occurred in plasma volume (Evans Blue method) and thiocyanate space over the experimental period. Total blood volume decreased more than plasma volume. Although the concentration of total plasma protein and sodium decreased with the fall in plasma volume. No relationship was found between fluid volume changes and the arterial pressure or transverse diameter of the heart.

WAIFE

Pulaski, J. E.: Perirenal Lymphangioma Causing Hypertension. Ann. Int. Med. **33**: 234 (July), 1950.

The author describes a case of hypertension in a 47 year old man caused by a perirenal cavernous lymphangioma compressing the left renal vessels and pelvis. Atrophic pyelonephritis of the left kidney, supposedly secondary to compression of the pelvis by the tumor, was considered to be the underlying cause. The lesion was not suspected during life. The cause of death was a large intracerebral hemorrhage secondary to the hypertension.

WENDKOS

Burkland, C. E., Goodwin, W. E., and Leadbetter, W. F.: Cure of Hypertension by Nephrectomy. A Ten-Year Follow-up of a Case. Surgery **28**: 67 (July), 1950.

The authors report a case of a 6 year old Negro boy, with hypertension from the age of 6 months, in whom an ectopic pelvic kidney was found. A nephrectomy was carried out; the kidney was described as hypoplastic, with the main artery partially occluded by a mass of smooth muscle. Following operation the blood pressure fell promptly from an average of 155/105 to a normal level. This type of change persisted during the subsequent 10 years. It is believed that the case represents a definite cure by nephrectomy of hypertension caused by unilateral renal disease. Of the other reports in the literature of hypertension treated by nephrectomy, the most common pathologic condition found in the kidney was chronic pyelonephritis, with marked atrophy of this organ. Only a few of these cases were cured or benefited by nephrectomy, probably because the other kidney was also involved in the process, or

because the condition was not discovered sufficiently early for a good result to follow from surgery.

Certain criteria are essential in the proper selection of patients with hypertension for whom nephrectomy is indicated. The diseased kidney should be functionless or its function greatly diminished, while the opposite kidney should function normally. Furthermore, the hypertension should be of short duration.

ABRAMSON

Wilkins, R. W., Greer, W. E. R., Culbertson, J. W., Halperin, M. H., Litter, J., Burnett, C. H., and Smithwick, R. H.: Extensive Laboratory Studies of a Patient with Pheochromocytoma before and after Successful Operation, with a Note on the Trial of Piperidylmethyl Benzodioxane to Differentiate Such Conditions from Essential Hypertensive Vascular Disease. Arch. Int. Med. **86:** 51 (July), 1950.

Extensive clinical and laboratory studies of a patient with pheochromocytoma before operation revealed elevation in arterial blood pressure, hypertensive vascular retinopathy, postural tachycardia, intermittent fever, hyperhidrosis, elevated basal metabolism, elevated fasting blood sugar, reduced dextrose tolerance, increased cardiac output, increased hepatic portal blood flow and oxygen consumption, intermittent albuminuria and glycosuria, decreased renal blood flow and elevated filtration fraction, positive reactions to histamine and benzodioxane tests and slightly decreased sensitivity to small intravenous injections of epinepehrine. After successful removal of the tumor, all these abnormalities disappeared except for the hypertensive pattern of renal function as measured by clearance technics. Postoperatively, electrocardiographic evidence was found of a myocardial infarction of the posterior wall, which probably occurred during the hypotensive postoperative period. The patient has remained asymptomatic.

Trial of piperidylmethyl benzodioxane as a diagnostic test agent for pheochromocytoma in 75 patients with hypertensive vascular disease has not proved it to be uniformly reliable or safe.

BERNSTEIN

Goldenberg, M.: Pheochromocytoma. J. A. M. A. **143:** 1139 (July), 1950.

The normal adrenal medulla and pheochromocytomas have been shown to contain not only epinephrine but also varying amounts of the corresponding primary amine, norepinephrine (Arterenol). This substance produces hemodynamic changes in man which are quite different from those that follow administration of epinephrine. The authors, therefore, decided to investigate the blocking effect of benzodioxane upon Arterenol-induced hypertension. Experiments were carried out in 19 normotensive subjects in whom a significant elevation of blood pressure had been produced by the intravenous infusion of l-Arterenol. The administration of benzodioxane diminished the pressor effect of the drug, although to a lesser degree than that produced by epinephrine. It was concluded, therefore, that the benzodioxane test is equally suitable for diagnosis of hypertension due to circulating epinephrine or to Arterenol.

The authors pointed out that no proof of a false positive result has been reported using the benzodioxane test. Nor has any persistent damage resulted from the administration of the drug. However, several alarming reactions have followed its use in hypertensive patients.

ABRAMSON

Suarez, R. M.: Incidence of Hypertension in Puerto Rico. Ann. Int. Med. **33:** 346 (July), 1950.

In a series of 3,081 cardiovascular patients observed in Puerto Rico, 957 (31.6 per cent) showed hypertensive cardiovascular disease. The latter figure is higher than that reported for a similar study in Mexico, Argentina, and the New England States, but lower than that of New York, Virginia, and Louisiana. Malignant hypertension was less common in Puerto Rico (2.7 per cent) than in New York (5 per cent). It appears from this study that climate is definitely not a deciding factor, and that diet, though it may play a secondary role, is far from being the essential factor in the genesis of essential hypertension.

WENDKOS

PATHOLOGIC PHYSIOLOGY

Van Dongen, K., and Taal, A.: Remarks on the Mechanism of Heart Fibrillation. Arch. internat. de pharmacodyn. et de therap. **81:** 129 (Feb.), 1950.

The authors report their work on decerebrated cats and rabbits (vagus nerves cut, stellate ganglia extirpated) and the isolated frog's heart. The antifibrillatory action of the substances they used could not be explained by alteration of the refractory period and conduction time because an antifibrillatory action was present with lengthening, shortening, or no action at all on these properties. The complete correlation between suppression of the heterotopic rhythms and neutralization of fibrillation suggests that fibrillation has its origin in one or more heterotopic centers, continuously giving rise to new stimuli in high frequency. The chemical grouping CH_2—CH_2—$N(C_2H_5)_2$, present in a number of antifibrillatory drugs (novocaine, atabrine F1262, and hydrastinine), is not present in all antifibrillatory drugs. The antifibrillatory drugs, in doses used by the authors experimentally, did not show a general antagonism to adrenaline and acetylcholine.

LECKS

Beling, C. A., Bosch, D. T., and Morton, T. V., Jr.: Blood Volume Determinations in Surgery; An

Analysis of 100 Cases. Surg., Gynec., & Obst. **90**: 686 (June), 1950.

Blood volume studies, using T 1824, were performed in 100 consecutive patients who were to undergo major surgery in an attempt to evaluate preoperative status through a determination of the extent of blood volume deficit. In 60 per cent of the cases, significant red blood cell deficits were found as well as reductions in plasma water, hemoglobin, circulating protein, and body protein. The authors considered a deficit of 10 per cent of the normal blood volume a significant amount and a patient with this abnormality a questionable risk. All individuals having a greater deficit than this were classified as poor surgical risks. In one group, replacement by transfusion could be done during operation. However, in a second group, this was necessary prior to surgery.

It was concluded that quantitative replacement of the circulating blood before operation results in reduced operative risk, lessened morbidity, and lowered mortality. The degree of deficit can only be determined by a study of the actual blood volume, since ordinary laboratory procedures such as hemoglobin, hematocrit, erythrocytes, and plasma proteins, may be grossly misleading in this regard.

ABRAMSON

Allen, T. H., and Orahovats, P. D.: Combination of Toluidine Dye Isomers with Plasma Albumin. Am. J. Physiol. **161**: 473 (June), 1950.

The combination of two toluidine dyes, T 1824 (Evans blue) and T 1836 (Trypan blue), with plasma albumin were examined by an adsorption equilibrium procedure.

Both dyes differ considerably when plasma mixing curves are plotted; Trypan blue disappearing from the circulation five times faster than Evans blue. The procedures employed demonstrate that the T 1824 linkage to albumin is completed within seconds after injection. It is calculated that upon injection into a vein, at least 395 of every 1,000 anions immediately combine with albumin. The blood flowing to the right auricle binds another 600 anions. The disappearance rate of the dye when corrected for blood removed is 4.5 per cent per hour, or 7.9×10^{-7} moles per hour, of which 3.2×10^{-7} moles per hour are recovered in lymph fluid. The final loss of T 1824 from the vascular system may be used as an index of albumin clearance. Trypan blue (T 1836) does not combine as readily with albumin, and upon injection into the blood a perceptible fraction escapes from the circulation. The maximum number of molecules of Evans blue anion that combine with one molecule of albumin is 11, whereas it is only 2 for Trypan blue.

HECHT

Vanremoortere, E., Dalem, J., Hanquet, M., and Mewissen, D.: Some Observations on Fibrillation and Defibrillation of the Ventricles. Arch. Internat. d. pharmacodyn. et de therap. **83**: 342 (July), 1950.

The authors studied the effect of various types of electrical stimulation on the dog heart in situ. Application of direct current (25 milliamperes) was invariably followed by permanent ventricular fibrillation. The same was seen following stimulation by alternating current of 30 to 80 milliamperes. However, if the latter stimulation was of only short duration, but not less than one second, fibrillation appeared but stopped spontaneously following interruption of the current. Defibrillation by electric shocks could be accomplished even after fibrillation had lasted 45 minutes provided the coronary circulation of the animal had been maintained by cross circulation with another animal. In one such instance defibrillation occurred spontaneously after 20 minutes.

Contrary to reports in the literature, the author observed a beneficial effect of adrenaline upon the failure of circulation which usually follows the cessation of ventricular fibrillation.

PICK

Baez, S., Mazur, A., and Shorr, E.: Hepatorenal Factors in Circulatory Homeostasis. XX: Antidiuretic Action of Hepatic Vasodepressor, VDM (Ferritin). Am. J. Physiol. **162**: 198 (July), 1950.

A marked reduction in urine excretion followed the intravenous injection of the vasodepressor material VDM in hydrated rabbits and dogs. A similar antidiuretic effect was achieved by small doses (150 to 300 mg.) of crystallized ferritin and the iron-free moiety apoferritin. The phenomenon is not related to changes in systemic blood pressure, nor to renal injury resulting from foreign protein reactions.

In several instances progressive refractoriness to repeated injections of heterologous ferritin appeared to be related to immunologic resistance associated with the development of precipitins. A similar refractoriness to homologous ferritin is not explained. The antidiuretic properties of VDM (ferritin) are of interest because ferritin can be demonstrated in the blood in conditions associated with oliguria.

HECHT

Huff, R. L., Hennessy, T. G., Austin, R. E., Garcia, J. F., Roberts, P. M., and Lawrence, J. H.: Plasma and Red Cell Iron Turnover in Normal Subjects and in Patients Having Various Hematopoietic Disorders. J. Clin. Investigation **29**: 1041 (August), 1950.

Iron tagged with Fe^{59} was administered intravenously to 75 subjects and its concentration determined as a function of time. Plasma iron turnover was increased in polycythemia, leukemia, pernicious anemia, and hemolytic anemia. The excess of turnover rate of plasma iron in a pernicious anemia patient in relapse returned to almost normal with therapy. Ra-

diotherapy reduced the excessive turnover rate of plasma iron in polycythemia vera. The authors conclude that the turnover rate of plasma iron is a much more sensitive indicator of iron metabolic abnormalities than plasma iron determinations alone.

WAIFE

Scherf, D., Morgenbesser, L. J., Nightingale, F. J., and Schaeffeler, K. T.: Mechanism of Ventricular Fibrillation. Cardiologia **16**: 232, 1950.

The authors used local application of aconitine to the surface of the heart, a method previously described by one of them for the production of auricular tachycardia and fibrillation, to study ventricular flutter and fibrillation. Rapid ectopic impulse formation in the ventricles, if appearing at a rate of about 300 per minute (ventricular tachycardia and ventricular flutter) could be transiently stopped by cooling the area to which aconitine had been applied. Ventricular fibrillation occurring at a rate of about 600 per minute was not affected by cooling. The transition of ventricular flutter into fibrillation occurred with a sudden change of the electrocardiographic contour of the ectopic beats. The authors conclude that one rapid center activitated by aconitine stimulates other more remote centers, the action of which results in ventricular fibrillation.

PICK

PATHOLOGY

Klemperer, P., Gueft, B., Lee, S. L., Leuchtenberger, C., and Pollister, A.: Cytochemical Changes of Acute Lupus Erythematosus. Arch. Path. **49**: 503 (May), 1950.

The authors studied the histochemical nature of the "hematoxylin-stained bodies" first observed by Gross in the valvular vegetations in Libman-Sacks disease, and later seen by others in lymph nodes and kidneys of acute lupus erythematosus. The report is based on a review of 35 cases of this disease. The authors found these apparently pathognomonic changes in 32 of the 35 cases, most frequently in endocardial and kidney sections, and to a lesser degree in the spleen and lymph nodes. In the last 4 cases, involvement of several sites was noted, and the authors believe that further study will reveal this to be the usual finding. They emphasize that these hematoxylin purple-stained bodies, seen either as the residual of single mesenchymal cells, or in great masses deeply stained within valvular vegetations, are entirely without structure. Nuclei cannot be seen and transition through necrobiotic changes, such as karyorrhexis and pyknosis, is wanting.

These bodies, in the opinion of the authors, originate in an alteration of the nuclei of mesenchymal cells that is characteristic for lupus erythematosus. Histochemical tests prove that they contain desoxyribose nucleic acid. This substance is partially depolymerized in the course of the disease in an obscure manner. These morphologic changes have been noted in a lymph node biopsy and also in bone marrow aspirates in patients with lupus erythematosus.

GOULEY

Lenegre, J., and Neel, J.: Pulmonary Embolism without Infarction. Arch. d. mal. du coeur **43**: 385 (May), 1950.

An analysis of autopsy data of 500 cases with heart disease revealed the presence of single or multiple pulmonary emboli in 173 instances. In more than one third of the observations, the embolization was not followed by pulmonary infarction. The clinical picture of the latter cases was misleading due to the absence of typical physical and radiologic signs of pulmonary infarction, and diagnosis could only be made post mortem. The hemodynamic consequences, however, were similar to those seen in a pulmonary embolus with infarction: development of an acute cor pulmonale with sudden pulmonary hypertension, acute dilatation of the right ventricle, and a more or less typical electrocardiographic pattern. The macroscopic appearance of the lungs may remain normal even with occlusion of the main vessel. The mechanisms acting in pulmonary embolization (or thrombosis) without infarction remain obscure.

PICK

Oppenheim, M.: Myocardosis in Liver Cirrhosis. Schweiz med. Wchnschr. **80**: 795 (July), 1950.

The author reports 168 cases of cirrhosis of the liver, 78 with autopsy, which were studied for the presence of degenerative changes in the myocardium. Clinical criteria suggestive of myocardial involvement were dyspnea, cyanosis, an abnormal electrocardiogram, and refractoriness to digitalis therapy. Alterations of the myocardium could be demonstrated clinically in the majority of the living patients and histologically in 100 per cent of the autopsied cases. All cases had abnormal protein values in the blood. There was a definite correlation between the degree of hypoproteinemia, the abnormality in the electrocardiogram, and the prognosis of the patients.

The author concludes that degenerative changes of the myocardium, found frequently in cirrhosis of the liver, represent a hepatogenic metabolic disease of the heart.

PICK

PHARMACOLOGY

Kartun, P., Paris, P., Nory, J., and Bousquet: Immediate Circulatory Action of an Intravenously Administered Mercurial Diuretic. Arch d. mal du coeur **43**: 133 (Feb.), 1950.

A fall in venous pressure, right auricular and right ventricular pressures was observed following the injection of from 1 to 4 cc. of a mercurial diuretic (Novurit) in 22 cases of congestive heart failure. A

fall in abnormally elevated pressures was observed when failure was pronounced, and was more striking in hypertensive and rheumatic heart disease than in chronic cor pulmonale. No effect was noted in constrictive pericarditis.

This direct cardiac effect is assumed to be caused by abrupt changes in venous inflow secondary to a peripheral effect of the diuretic. The value of intravenous mercurial diuretics in the treatment of acute pulmonary edema is stressed.

HECHT

Assali, N. S., Brust, A. A., Garber, S. T., and Ferris, E. B.: Comparative Study of the Effects of Tetraethylammonium Chloride and Veratrum Viride on Blood Pressure in Normal and Toxemic Pregnancy. J. Clin. Investigation **29**: 290 (March), 1950.

The blood pressure responses to tetraethylammonium chloride (TEA) and veratrum in normal pregnancy and in toxemia are in striking contrast. In toxemia TEA does not lower the blood pressure, while veratrum consistently lowers the toxemic blood pressure to hypotensive levels; however, in normal pregnancy, veratrum in the same dosage causes only a negligible response, while TEA invariably produces a marked depressor effect.

Bradycardia, nausea, and vomiting followed veratrum administration but was independent of the depressor action of the drug. Administration of TEA at the time of this maximum effect immediately eliminated the concomitant manifestations of veratrum.

The opposing actions of TEA and veratrum plus the consistent depressor effects of the standard dose of veratrum (0.2 cc.) in toxemia allow for a further elaboration of blood pressure assay for diagnostic purposes in borderline toxemia.

WAIFE

Heller, J. H., Setlow, R. B., Mylon, E.: Fluorimetric Studies of Epinephrine and Arterenol. Am. J. Physiol. **161**: 268 (May), 1950.

Spectrographic studies demonstrate that the fluorescence produced by epinephrine in alkaline solution has a maximum at 5400 A. The fluorescence of a comparable l-arterenol solution is ten times weaker and slightly more toward the violet. Bifluorescence, a complication of irradiation of plasma, is reduced by the use of monochromatic incident light and selective filters. The great decrease in light transmission caused by highly selective filter arrangements is compensated for by a photo-multiplier-amplifier combination. Reaction curves show that the fluorescent substance is destroyed at a faster rate than it is formed. Adrenochrome may be an intermediate stage in the formation of a fluorescent substance from epinephrine. Strong alkalinity and the presence of oxygen are two recognized conditions necessary in this reaction. If oxygen is in excess, the fluorescent substance is rapidly destroyed.

HECHT

Ryan, J. M., and Zimmerman, H. A.: Effect of Digitalis in Patients with Enlarged Hearts and Sinus Rhythm but without Congestive Failure. Am. J. Med. **8**: 808 (June), 1950.

The authors studied cardiac outputs by the direct Fick principle in 8 patients with enlarged hearts and sinus rhythm but no congestive failure (determined not only clinically, but by appraisal of the right auricular pressure and the right ventricular diastolic pressure.) Three had hypertensive heart disease, one had rheumatic heart disease, 2 had cor pulmonale, 1 syphilitic aortic insufficiency, and 1 coronary artery disease. In all these patients the cardiac outputs, the right auricular pressures, and the right ventricular diastolic pressures were within normal range. After rapid digitalization followed by a maintenance dose of whole leaf, the cardiac output was increased significantly in 1 patient and remained essentially the same in 7. There was no consistent change in the right auricular mean pressure. The pulmonary artery, femoral artery, and right ventricular pressures, the heart rate, stroke volume, and A-V oxygen differences remained essentially unchanged.

BELLET

King, B. D., and Dripps, R. D.: Use of Methoxamine for Maintenance of the Circulation during Spinal Anesthesia. Surg., Gynec. & Obst. **90**: 659 (June), 1950.

Methoxamine, a new pressor drug, was used in more than 800 patients in an attempt to prevent the hypotension which frequently follows spinal anesthesia. The drug appeared to have its pressor action predominantly on the peripheral vascular system at the effector cells or through the vasomotor system, or both. No cerebral cortical stimulation was noticed. The pharmocologic reactions resembled those of Neosynephrin, although the effect of the drug was more prolonged. When administered intravenously during the period of hypotension produced by spinal anesthesia, methoxamine produced an increase in peripheral resistance, a sustained increase in blood pressure, and a bradycardia. When given intramuscularly prior to the anesthesia, no significant fall in blood pressure occurred.

It was concluded that methoxamine is effective in minimizing or eliminating the decrease in blood pressure associated with spinal anesthesia, and appears to have certain advantages over some of the other drugs used for this purpose.

ABRAMSON

Samuels, S. S., and Padernacht, E. D.: A New Vasodilator (Roniacol). A Preliminary Report. Angiology **1**: 236 (June), 1950.

One hundred patients with peripheral arterial disease received a new vasodilating drug, 3-pyridinemethanol (Roniacol). The drug induces a subjective feeling of warmth in all extremities and appears to alleviate intermittent claudication. The dosage schedule is 100 mg. three times a day, and the effect is enhanced if an additional 100 mg. are given intramuscularly each day. Except for occasional temporary nausea, there were no annoying side effects.

WESSLER

Enderby, G. E. H.: Controlled Circulation with Hypotensive Drugs and Posture to Reduce Bleeding in Surgery. Preliminary Results with Pentamethonium Iodide. Lancet **1**: 1145 (June), 1950.

The author feels that it is the anesthetist's duty to lower the blood pressure of the surgical patient to keep bleeding at a minimum. He quotes Gillies who stated that a systolic blood pressure of 60 mm. is sufficient to maintain an adequate cellular capillary circulation, provided vasodilatation is insured. The author attempted to produce this effect by the use of pentamethonium iodide and similar drugs which paralyze the autonomic ganglia in lieu of the spinal technic which he feels is dangerous. He feels that because these drugs are not pure sympathetic paralyzants, they are not as adequate as a total sympathetic block. Gravitational pooling of blood in the legs, as recommended by Griffiths and Gillies, is of major importance as an adjunct to the medication recommended. The author discusses the varied diagnoses of patients subjected to anesthesia, and the results obtained by the use of both drugs and gravitational pooling in 50 patients. He feels that where full use was made of the effects of gravity, a valuable reduction in bleeding was obtained. In an addendum, he points out that for best results, an attempt should be made to reduce the blood pressure to 60 mm. in all cases, for, with pentamethonium iodide, the reduction often falls short of this by a small margin. He mentions the use of methedrine to counteract excessive blood pressure reduction; this was given into veins located in the dependent parts.

TANDOWSKY

Orbach, E. J., and Petretti, A. K.: The Thrombogenic Property of Foam of a Synthetic Anionic Detergent (Sodium Tetradecyl Sulfate N.N.R.). Angiology **1**: 237 (June), 1950.

The authors describe their technic for the sclerotherapy of varicose veins, using foam produced by a solution of sodium tetradecyl sulfate N.N.R. Dilution of the solution with blood is avoided, the amount of the drug used is extremely small, and none of the usual side reactions or untoward effects of sclerotherapy are encountered. Satisfactory results were obtained in 91.3 per cent of the varicosities injected.

WESSLER

Kadner, C. G., Dean, W. I., Chambers, D. F., and Poliquin, R. G.: The Curare-like Effect of Thiamine Hydrochloride Solution on Vagal Inhibition of the Frog Heart. Science **112**: 84 (July 21), 1950.

The authors found that vagal stimulation was effective in stopping the beat of the exposed frog heart when dilutions of thiamine hydrochloride greater than 1:2000 were applied. Dilutions of 1:2000, however, resulted in complete blocking of the vagal inhibition.

SACHS

Ruskin, A., Rabinowitz, H., and Damiani, M.: A Comparative Study of Human Cutaneous Reactivity to Thiomerin and Other Mercurial Diuretics. J. Lab. & Clin. Med. **36**: 1 (July), 1950.

This study was done to evaluate the comparative local toxic actions of Mercuzanthin, Salyrgan-theophylline, Mercuhydrin and Thiomerin in the human skin. Thiomerin in intracutaneous tests in 53 human subjects caused slighter and more transitory reactions than Mercuhydrin, Salyrgan-theophylline and Mercuzanthin. Subcutaneous Thiomerin injections produced slight tenderness lasting less than two hours in four per cent of the subjects and small transient infiltrations in 6 per cent. The subcutaneous reactions to Mercuhydrin were more lasting and severe.

The relative local innocuousness of Thiomerin, together with its much lower cardiotoxicity and unimpaired diuretic effect when compared with other mercurial diuretics, provides a firm basis for its clinical adoption as the mercurial diuretic of choice for subcutaneous, intramuscular, or intravenous use.

MINTZ

Stein, I., and Weinstein, J.: Further Studies of the Effect of Ergonovine on the Coronary Circulation. J. Lab. & Clin. Med. **36**: 66 (July), 1950.

The report includes more detailed studies of ergonovine on the coronary circulation together with the effects of nitroglycerine and exercise. A total of 66 tests were performed on 30 subjects, 15 of whom were not considered clinically to have coronary artery insufficiency. The dosage of the drug varied between 0.05 and 0.6 mg. and was injected intravenously. The only toxic effect was transient nausea in 3 cases. Electrocardiograms were taken as the drug was administered and after intervals of 1, 5, 10 and 15 minutes.

The criteria which were adopted in the evaluation of positive results were essentially similar to those used by Levy, Master and Grossman, and Weinstein and Katz. The test was considered positive when there was S-T segment depression of 0.75 mm. in a limb lead and 1.50 mm. in a chest lead; significant T wave alterations in leads I, II, or V_4; the development of numerous premature beats; the occurrence of chest pain which was relieved by

nitroglycerin. The ergonovine test was positive in all of the 15 cases in which a clinical diagnosis of coronary artery disease was made. In 6 of these cases, the exercise test was negative.

It was assumed ergonovine has a direct effect on the coronary blood vessels, producing spasm. The nullification of the effect by the simultaneous use of nitroglycerin and the lack of pulse and blood pressure changes favors this assumption.

Although no significant toxic effects were obtained even when large doses of ergonovine were given to patients with pre-existing electrocardiographic abnormalities, the authors advise that patients should be carefully selected and precautions taken by having nitroglycerin or amyl nitrite on hand during the test.

MINTZ

Jaffe, H. L., Master, A. M., and Dorrance. W.: The Salt Depletion Syndrome following Mercurial Diuresis in Elderly Persons. Am. J. M. Sc. **220:** 60 (July), 1950.

The authors present 8 cases of salt depletion and dehydration consequent to the administration of mercurial diuretics to elderly patients. It is pointed out that this reaction may be fatal. It is stated that the frequency of such reactions appears to have increased following the introduction of intensive, daily mercurial therapy. The authors recommend that the dose in elderly persons should be 1 ml. given at intervals of several days, and that the blood urea nitrogen should be determined twice a week. The induction of symptoms of prostatism by mercurial diuresis is also discussed.

DURANT

Lewin, N., and Aronoff, A.: Tuberculosis Pericarditis Treated with Streptomycin. Canad. M. A. J. **63:** 70 (July), 1950.

A 27 year old man with far advanced pulmonary tuberculosis, previously treated with pneumoperitoneum and left phrenic crush, developed severe chest pain and dyspnea together with roentgen evidence of cardiac enlargement. The configuration was characteristic of pericardial effusion. Although the diagnosis was not absolutely proved, it was considered to be a tuberculous pericarditis. Prompt improvement followed dihydrostreptomycin therapy, with a return of the temperature to normal within 12 to 18 hours and marked clinical and x-ray improvement within 7 days. There were two episodes of pericarditis with effusions, seemingly following pneumoperitoneum refills. On both occasions, streptomycin therapy led to prompt clinical improvement.

WAIFE

Houston, A. B., and Perry, W. F.: The Plasma Concentration of Quinidine after Oral Administration and its Effect on Auricular Fibrillation. Canad. M. A. J. **63:** 56 (July), 1950.

The quinidine content of plasma, urine, and feces was estimated by the photometric method of Brodie and Udenfriend, which is not specific for quinidine. Following oral ingestion of a single dose, a wide variation of plasma levels was noted in different subjects. In general, the maximum level occurred between two and four hours after ingestion. Only a small proportion of a given dose was found in the urine and feces. Well-sustained plasma levels were obtained on repeated doses at intervals of three to four hours. Ten subjects with auricular fibrillation received twelve trials of various dosage schedules. Plasma quinidine levels of 3 mg. per liter or more were obtained in 8 instances. In 5 of these, normal rhythm was restored. It was necessary to administer a dose of 0.4 gm. every three to four hours to maintain a level of 3 mg. per liter. The authors believe that a quinidine effect does not occur until the plasma concentration attains this or a higher value. They conclude that an adequate trial should consist of 0.4 gm. every three to four hours, to be increased by 0.2 gm. per dose each 24 hours up to tolerance.

WAIFE

Clarke, D. A., Modell, W., Greiner, T., Kwit, N. T., Gluck, J. L., and Gold, H.: The Dosage-Response Curve for the Comparison of Mercurial Diuretics. Am. J. M. Sc. **220:** 156 (August), 1950.

The dosage-response curve has become a standard device for the comparison of drugs in animals. Such curves provide not only quantitative, but qualitative information concerning agents in a comparison. The fact that this technic has not been generally utilized in studying drugs in man may account for the discordant results often seen in the clinical literature. It is pointed out that the conventional method of comparing mercurial diuretics is not sound. It is feasible to prepare satisfactory dosage-response curves for mercurial diuretics in patients with congestive failure. A dosage-response curve for Mercuhydrin is presented. This curve is based upon the response to 971 intravenous injections in 73 patients.

DURANT

Ray, C. T., Burch, G. E., Threefoot, S. A., and Kelly, F. J.: The Distribution of Radiomercury of a Mercurial Diuretic in Some of the Body Fluids of Man. Am. J. M. Sc. **220:** 160 (August), 1950.

Following a single intravenous injection, it was found that no measurable quantities of radiomercury entered the cerebrospinal fluid, sweat, gastric juice or erythrocytes, and only low concentrations were reached in the saliva, edema, peritoneal and pleural fluids. Relatively high concentrations were attained in the bile, but biliary excretion is not an important route of elimination in the presence of normal kidneys. Failure of mercury to accumulate in tissues in relatively large amounts arouses speculation concerning the diuretic action of the material through systemic action.

DURANT

Schaffer, A. I., Steinmann, R., and Scherf, D.: Intravenous Procaine: Its Effect on the Human Electrocardiogram and on Cardiac Arrhythmias. Cardiologia **16:** 342, 1950.

The authors studied the effect of intravenous procaine bihydrochloride on the electrocardiogram of patients without heart disease and on various types of cardiac irregularities. In one group 300 to 500 mg. of a 1 per cent saline solution were injected in 8 to 30 seconds. In another group, 100 mg. of a 1 per cent solution was injected within 4 seconds.

Changes in the contour of the electrocardiogram observed in some experiments were minimal and consisted in slight flattening of the T wave, and in one case, in prolongation of the Q-T interval. Some effect was noted in auricular flutter (slowing of the auricular rate and increase in ventricular rate). Procaine may also temporarily depress A-V and intraventricular conduction and produce auricular premature beats. The authors conclude that procaine, in the doses used, is not effective in the treatment of arrhythmias.

PICK

PHYSICAL SIGNS

Luisada, A. A., and Montes, L. P.: A Phonocardiographic Study of Apical Diastolic Murmurs Simulating Those of Mitral Stenosis. Ann. Int. Med. **33:** 56 (July), 1950.

In a selected group of patients, it was observed that an auricular or ventricular gallop associated with mitral or aortic insufficiency, or a split second sound associated with bundle branch block, or a late systolic or early diastolic snap associated with adhesive pericarditis can simulate the sounds of mitral stenosis but can be differentiated from the rheumatic lesion by phonocardiographic studies. In a second group of cases, the phonocardiograms revealed diastolic-presystolic vibrations indistinguishable from those of mitral stenosis; the functional nature of the murmur was revealed by either the subsequent clinical course or negative postmortem findings. This group included patients with aortic insufficiency (Austin Flint murmur), coronary heart disease, and auricular flutter.

WENDKOS

PHYSIOLOGY

Widdowson, E. M., and McCance, R. A.: The Effect of Rest in Bed on Plasma Volume, as Indicated by Hemoglobin and Hematocrit. Lancet **1:** 539 (March), 1950.

The authors studied the effect of bed rest on plasma volume in a series of hospitalized patients. After three days of recumbency a rise in hemoglobin and hematocrit levels was noted, this being interpreted as indicating a fall in the volume of the plasma. It was suggested that this was the result of protracted inactivity rather than recumbency.

ABRAMSON

McDowall, R. J. S.: The Responses of the Blood Vessels of the Muscles, with Special Reference to Their Central Control. J. Physiol. **3:** 1 (April), 1950.

Experiments were carried out in anesthetized cats to discover to what extent the blood vessels in the muscles are controlled centrally and how this control affects their responses. The skin was removed from the hind limb, the latter then being placed in a plethysmograph.

After studying the volume changes produced by different procedures in the skinned limb, the author concluded that the control of the vessels of the muscles is very similar to that of vessels in the rest of the body. However, he found that the degrees of stimulation which affected the skin vessels did not necessarily cause any change in those of the muscle. Furthermore, the vessels in muscle were not as sensitive to depressor reflexes as those in the skin. Although the vessels in the muscles were found to dilate after administration of adrenaline and noradrenaline, the author believes that normally they are tonically constricted by impulses spreading over the fibers of the lumbar sympathetic cord.

ABRAMSON

Mendlowitz, M.: Calorimetric Measure of Blood Flow. Angiology **1:** 247, (June), 1950.

Digital calorimetry is an indirect technic for measuring digital blood flow. In this paper the validity of the method is analyzed in detail. It is concluded that the maximum error is so small and the normal range so narrow, that it is possible to distinguish between normal and abnormal responses.

WESSLER

Suckling, E. E., Brooks, C. M., Orias, O., Gilbert, J. L., and Siebens, A. A.: Determination of Excitability of Mammalian Heart at Intervals throughout Cardiac Cycle. Am. J. Physiol. **162:** 213 (July), 1950.

An oscillator system is described which permits control of the rate of the beating heart in dogs. A driving stimulus at rates between 0.1 and 13 milliseconds is applied by a square wave generator to the surface of the myocardium after obliteration of the sinoatrial node.

In determining the excitability of the heart, strength-duration curves are obtained at various intervals throughout the cardiac cycle. The limits of the refractory period vary with the duration of the stimulus; short stimuli indicate long absolute and short relative refractory periods, while long duration stimuli have opposite effects. Falsely low thresholds are obtained when the testing stimuli are close

together, suggesting the presence of long persistent local excitatory states. Hyperexcitability early in the relative refractory period could be demonstrated.

HECHT

Everett, N. B., and Johnson, R. J.: Use of Radioactive Phosphorus in Studies of Fetal Circulation. Am. J. Physiol. **162:** 147 (July), 1950.

The intracardiac fetal circulation of guinea pigs and dogs delivered by caesarian section near term was examined by the use of radioactive phosphorus (P^{32}). Blood was simultaneously taken from the right and left ventricles at successive intervals after P^{32}-labeled saline was injected into (a) the umbilical vein and (b) external jugular vein.

Within a mean of 16.7 seconds, three-fourths of the tracer saline injected into the umbilical vein was delivered to the left ventricle, and one fourth recovered from the right ventricle. Within a mean of 16.2 seconds, three-fourths of the tracer material injected in the external jugular vein was recovered from the right ventricle, and only one-fourth delivered to the left cavity. Measurement of circulation time between umbilical vein and artery ruled out the possibility of recirculation.

The conclusion is drawn that three-fourths of the blood returning to the heart from the umbilical vein in fetal circulation of guinea pigs and dogs passes directly through the foramen ovale to the left auricle and ventricle. Of the blood returning via the external jugular vein, only one-fourth traverses the foramen ovale.

HECHT

Olsen, N. S., and Nuetzel, J. A.: Resistance to Small Doses of Insulin in Various Clinical Conditions. J. Clin. Investigation **29:** 862 (July), 1950.

A group of subjects received $\frac{1}{40}$ unit of insulin per Kg. actual body weight. Blood sugar was determined at 15, 30, and 60 minutes. The blood sugar response was normal for 38 patients with essential hypertension. However, 11 malignant hypertensive subjects were insulin resistant. Insulin resistance was also found in collagen, neoplastic, and infectious diseases.

WAIFE

Henry, J. P., and Gauer, O. H.: The Influence of Temperature upon Venous Pressure in the Foot. J. Clin. Investigation **29:** 855 (July), 1950.

The pressure in a dorsal vein of the foot was determined directly in 12 adult male subjects. During vasodilatation induced by both local and environmental heat, vigorous walking movements failed to reduce mean venous pressure below 70 mm. Hg. The rate of fluid accumulation at these relatively high levels of venous pressure may exceed the capacity of lymphatic removal. This may help to explain the ankle edema in hot weather. In the comfortable temperature zone, less activity is required to effect a similar reduction in venous pressure. In cool temperatures, normal involuntary postural movements may reduce the pressure to 50 mm. Hg. This level approximates osmotic and tissue pressure. With vasodilatation the pressure gradient increases.

WAIFE

Kerslake, D. M., and Cooper, K. E.: Vasodilatation in the Hand in Response to Heating the Skin Elsewhere. Clin. Sc. **9:** 31, 1950.

The mechanism involved in indirect vasodilatation produced by application of heat to distant portions of the body was investigated in a series of normal patients. Blood flow was measured in the hand using a venous occlusion plethysmograph while heat was applied to the trunk and legs by means of a radiant heat cradle. It was found that an increase in circulation in the hand occurred within an average of 13 seconds after the beginning of heating. In experiments in which heat was applied to the legs alone, the application of pressure to the thighs, high enough to interfere with arterial inflow into the lower extremities, did not prevent the vasodilator response from occurring in the hands.

The authors concluded that the increase in circulation in the hands was due to afferent nervous impulses arising in the heated skin of the trunk or legs and not the result of warmed blood reaching the temperature-regulating center in the brain.

ABRAMSON

Vanremoortere, E.: The Inspiratory Acceleration of the Heart Rate in Man. Acta cardiol. **5:** 163, 1950.

In order to explain the inspiratory acceleration of the heart rate, three theories are classically referred to, namely the "inter-central association," the Bainbridge reflex, and also the phenomenon originally described by E. Hering in 1871: experimental distension of the lungs stimulates the pulmonary endings of the vagus nerve, thus giving rise to reflex tachycardia.

The existence of this reflex has been demonstrated by many investigators who, in addition, agree unanimously on the following fact: the acceleration of the heart persists as long as the lungs are kept inflated. The author presents evidence which tends to disprove Hering's theory.

His results show that the extent of pulmonary distension does not, under physiologic conditions, influence the heart rate in man:

(1) After the acceleration produced by deep inspiration, the heart immediately slows down even if the subject does not exhale. This decrease in rate is identical in all respects to that accompanying expiration.

(2) When the subject holds his breath after a deep

inspiration and as soon as the inspiratory acceleration has subsided, the heart rate returns to the "normal" value existing during shallow breathing. The following expiration does not produce any slowing of the pulse.

(3) The average heart rate is identical when the subject holds his breath after expiration or inspiration.

These results seem to warrant the conclusion that the Hering lung-heart reflex, as is described in the literature, does not play any part in the inspiratory acceleration of the human heart.

AUTHORS

RHEUMATIC FEVER

Brewer, T. F.: Rheumatic Fever and Rheumatic Carditis Treated with "Pregnancy" Hormones. Connecticut M. J. **14:** 489 (June), 1950.

Over a 12 year period the author treated 97 patients with various combinations of hormones. The recommended regime consists of the simultaneous administration of 500 mg. of progesterone and 33.3 mg. of estradiol. The intervals between injections ranged from four to eight days. For sustained satisfactory results from two to seven injections are necessary. The author reports a satisfactory response in 57.7 per cent of the 97 cases, a slight response in 15.5 per cent, and no response in 26.8 per cent. No serious side effects were noted. A response was considered satisfactory when the temperature, sedimentation rate, white blood count, electrocardiograms, and affected joints were normal.

WAIFE

Bradfield, J. Y., and Hejtmancik, M. R.: Cardiac Disease and Rheumatoid Arthritis. Arch. Int. Med. **86:** 1 (July), 1950.

In a series of 45 cases with rheumatoid arthritis 16 (35.8 per cent) showed evidences suggestive of heart disease, and 7 (15.7 per cent) had definite clinical, roentgenographic, and/or electrocardiographic evidence of heart disease which could be explained on no other basis than relation to the rheumatoid arthritis. These patients with "rheumatoid heart disease" tolerate the cardiac lesions well because they are of a mild degree and because their activity is limited by their arthropathies. The authors feel that there is strong indirect evidence that rheumatoid arthritis and rheumatic fever are different manifestations of one fundamental morbid process, and they believe this to be allergic in character.

BERNSTEIN

Bell, G. I., Bell, R. E., and Wilson, D. R.: Rheumatic Pancarditis Treated with Cortisone. Canad. M. A. J. **63:** 63 (July), 1950.

An 18 year old male with rheumatic fever developed severe pancarditis associated with pericardial friction rub, gallop rhythm, and congestive heart failure. A large initial dose (2 Gm.) of cortisone was administered in the first 48 hours in divided doses. Therapy was continued with 200 mg. the following day, and 100 mg. daily for six days, concluding with 50 mg. daily for the last seven days. Within 48 hours after cortisone therapy was begun, the temperature became normal, and the gallop rhythm and friction rub disappeared. Dyspnea and tachycardia rapidly subsided. Transient auricular fibrillation appeared on the third day of treatment and lasted for 24 hours. When cortisone was stopped, salicylates did not prevent the recurrence of gallop rhythm and fever.

WAIFE

Taran, L. M., and Szilagyi, N.: Oxygen Therapy in Acute Rheumatic Carditis in Children. Bull. New York Acad. Med. **26:** 461 (July), 1950.

Over a period of six years 121 children received 11,000 days of oxygen therapy, or an average of 90 days per patient. Special oxygen chambers were used with the following average concentrations: oxygen, 50 per cent; carbon dioxide, 1.5 per cent; humidity, 75 per cent. The temperature averaged 66 F. and the barometric pressure was normal.

Fifty-eight children responded well to oxygen and showed marked clinical improvement. The remaining 63 were not improved or presented signs of marked intolerance to this treatment.

Signs of improvement included: increased weight and appetite, improved coloring and emotional behavior, drop in temperature and narrowing of daily temperature fluctuations, slowed respiration rate, drop in pulse rate, more stable cardiac rate, quickened subsidence of gallop rhythm where present, subsidence of murmurs, relief of anginal attacks and dyspnea on exertion, and subsidence of conduction disturbances. The unknown mechanisms by which salutary effects are attained in rheumatic carditis are under investigation.

WHITE

Massell, B. F., Coen, W. D., and Jones, T. D.: Artificially Induced Subcutaneous Nodules in Rheumatic Fever Patients. Pediatrics **5:** 909 (June), 1950.

In 340 rheumatic patients and in 185 control subjects, the authors attempted to induce subcutaneous nodules by injecting 2 to 4 cc. of blood taken from the antecubital veins into the region of the olecranon process of the opposite elbow. The rheumatic patients were divided into 4 groups, depending on the activity of the disease at the time of the test. In the quiescent group, 15 per cent developed subcutaneous nodules, whereas nodules were induced in 18 per cent of the group with mild activity, 71 per cent of those with moderate activity, and 86 per cent of those with severe rheumatic disease. The more active the rheumatic process, the larger the size of the nodule and the longer it remained palpable. In the control group 2.7 per

cent developed nodules; however, 4 cases had scarlet fever.

To determine whether the induced nodules were due to a factor in the blood or to the traumatizing effect alone, the patient's own blood was injected in one elbow and saline was injected in the other elbow. Saline was not as good an agent as blood for the induction of nodules. Blood from patients with active rheumatic fever produced nodules more often than did the patient's own blood. However, blood from healthy young adults produced nodules slightly more often than did the blood from patients with active rheumatic fever. One half cc. of hyaluronidase injected subcutaneously daily for four to five injections was found to induce subcutaneous nodules in 11 of 24 tests.

The authors conclude that the development of nodules results from injury to the subcutaneous fibrous tissue, and that the hypothesis of a nodule-stimulating substance present in the blood of active rheumatic patients is untenable. The fact that nodules have been induced in some rheumatic patients by the subcutaneous injection of hyaluronidase, and that trypsin has been shown by others to be an effective nodule-inducing agent, led them to suggest that enzymes may play a role in nodule formation.

MARGOLIES

Blanchard, K. C., Harvey, A. M., Howard, J. E., Kattus, A., Marshall, E. K., Newman, E. V., and Zubrod, C. G.: The Effects of 3-Hydroxy-2-phenylcinchoninic Acid upon Rheumatic Fever. Bull. Johns Hopkins Hosp. **87**: 50 (July), 1950.

Because 3-hydroxy-2-phenylcinchoninic acid (HPC) decreases urinary flow in diabetes insipidus, inhibits excretion by the renal tubule of phenol red and penicillin, increases excretion of uric acid, and reduces the ascorbic acid content of the rat adrenal, the authors felt that HPC might be of value in diseases responding to ACTH. Ten patients with acute rheumatic fever were given 20 mg. of HPC per Kg. of body weight on the first day, and 10 or 20 mg. per Kg. daily or every other day for 2 to 21 days. Fever, joint pain, and tenderness usually subsided within 24 hours. Swelling, however, persisted from 24 to 48 hours in 4 cases. Elevation of the sedimentation rate and marked electrocardiographic changes persisted during drug administration. In most cases these reverted to normal after the drug was stopped. Relapse occurred in 3 cases, 2 of which were re-treated without recurrence of rheumatic activity for three months. One patient died during the relapse. In two cases of disseminated lupus erythematosus, HPC showed some favorable effect. Side effects noticed were drug fever in one case, nausea in 10 per cent of the cases, and abdominal cramps in 5 per cent.

HPC could not be shown unequivocally to increase the output of the anterior pituitary or adrenal cortical hormones. HPC did not have an antipyretic effect in patients with nonrheumatic fevers. The mechanism of action of HPC has not been demonstrated.

MARGOLIES

ROENTGENOLOGY

Dotter, C. T., and Jackson, F. S.: Death following Angiocardiography. Radiology **54**: 527 (April), 1950.

Through a questionnaire sent to most of the general hospitals in the United States, Canada, Great Britain, and Sweden, the authors complied a fairly complete list of fatalities following angiocardiography. A total of 6,824 examinations was reported, with death in 26 cases. Of the latter, 3 were complicated by other factors and hence were not included in the analysis of the causes of death. No fatalities occurred in patients with normal hearts, except for 1 case suffering from renal arterial disease. In 21 patients congenital heart disease existed, 17 of these being cyanotic, and 5, extremely ill. The most common form of death was reported to be sudden respiratory arrest immediately or shortly following injection of the contrast medium. Necropsy examination was of little value. The incidence of death was higher in children, in patients with congenital heart disease, in those receiving larger doses of contrast material, and in those examined in the horizontal position.

ABRAMSON

Bingham, J. R., Ingelfinger, F. J., and Smithwick, R. H.: Effects of Sympathectomy on Abdominal Pain in Man. Gastroenterology **15**: 18 (May), 1950.

The authors utilized patients undergoing sympathectomy to study the distribution and course of the visceral sensory nerves in man. Intestinal pain was produced by inflating balloons in the small and large bowel, while biliary tract discomfort was elicited by perfusing saline under pressure through a T-tube in the common duct. Esophageal pain was produced by distending the middle and lower thirds of this organ.

Esophageal pain was described as a pressure or "knot" sensation and was generally experienced substernally. Duodenal pain, typically situated in the upper epigastrium, was of low intensity and well localized. It was described as burning, cramping or sickening. Jejunal and ileal pain was similar to that produced by pressure in the duodenum, except that it was situated lower in the abdomen. Biliary tract pain was also like duodenal pain. Following unilateral sympathectomy, stretching of the bowel produced pain which was referred to the contralateral side. After bilateral sympathectomy, distension pain was abolished.

This evidence suggests that the pain pathways from the jejunum may pass through the tenth, eleventh, and twelfth thoracic sympathetic ganglia,

and not invariably through the greater splanchnic nerves. In the case of the sympathectomized patient who still experiences pain from abdominal disorders, evidently other mechanisms and pathways account for this symptom.

ABRAMSON

Reynolds, L., Corrigan, K. E., and Haden, H. S.: The Use of the Cinefluorographic Method for Teaching Purposes. Am. J. Roentgenol. **63:** 902 (June), 1950.

The authors discuss the technical factors needed to record good motion picture images from a fluorescent screen. The type of screen, camera, and the total exposure of the patient to roentgen rays all present problems of their own. Adaptability for fast or slow motion is accomplished by a motor driven mechanism plus spring propulsion; variations in focal distance for general usage require the construction of a rail mount and suitable housing. The roentgen tube, its focal spot, and the target screen distance must meet the specific needs.

The authors consider the construction and use of such apparatus entirely practical and useful for recording organ motion or visualizing contrast medium in great vessels, as in angiocardiography. The illustrations presented indicate that it is an excellent teaching method. The authors also indicate that modern cinefluorography does not require excessive exposure to the patient and is entirely safe for the operators.

SCHWEDEL

Goulder, N. E., Carpender, W. J., and Levin, E.: X-Ray Treatment for Peptic Ulcer Does not Appear to Damage the Heart. Gastroenterology **15:** 264 (June), 1950.

The authors attempted to evaluate clinically the possibility of cardiac injury arising from x-ray irradiation of the gastric fundus. The portals employed for irradiation include, among other structures, a variable portion of the apex, lower left border, and diaphragmatic aspect of the heart.

Twelve duodenal ulcer patients were observed for a period of six weeks subsequent to the conclusion of irradiation treatment. Each patient was free of evidence of heart disease by history, physical examination, and chest fluoroscopy. There was no suggestion of cardiac injury as determined by clinical observation, orthodiagram, or development of persistent electrocardiographic abnormality. Serial electrocardiograms revealed minor variations, particularly in the terminal portion of the ventricular complex. These alterations were transient. It is concluded that irradiation therapy for peptic ulcer may be safely administered without causing clinically significant cardiac damage.

SCHWARTZ

Campbell, D. A., and Smith, R. G.: Arteriography in the Evaluation of Arteriosclerotic Vascular Insufficiency. Am. J. Surg. **80:** 76 (July), 1950.

On the basis of their experience with over 100 arteriograms in arteriosclerotic extremities, the authors established a classification which they considered of value in the choice and application of certain therapies.

The first type of change consists of obstruction due only to narrowing of the lumen, with some irregularity and constriction of the major vessels and an increase in collateral filling. The second group shows complete filling of major vessels of the thigh but complete occlusion of one or two of the three main vessels below the popliteal artery. Collateral filling may be considerably increased, especially below the knee. In the third classification there is complete occlusion of a segmental type, generally at the level of the femoral or popliteal arteries. In this group there is a patent collateral system sufficient to fill a major vessel below the point of obstruction. However, the blood is delivered to the tissues under decreased pressure. The fourth type shows complete occlusion of the anterior and posterior tibial and the peroneal arteries. Generally the amount of blood reaching the tissues of the foot is insufficient for the metabolic needs of the tissues. Unless the occlusion develops over a sufficiently long period to allow the small collaterals to take over the entire task of nourishing the foot, gangrene will occur. Finally in the fifth group, complete obstruction of the femoral, at its bifurcation, has occurred, leading to gangrene of the foot and leg.

According to the authors, arteriography does not irritate the intima sufficiently to initiate or propagate thrombi, nor does it produce vasospasm to any degree. It assists in determining the desirability of conservative therapy or of amputation, aids in determining the level of amputation, and is of use in selecting patients for lumbar sympathectomy.

ABRAMSON

SURGERY IN HEART AND VASCULAR SYSTEM

Dunning, E. J., and Jones, T. E.: Obstruction of the Duodenum by an Aneurysm of the Abdominal Aorta. Am. J. Surg. **79:** 848 (June), 1950.

To the 2 cases in the literature of duodenal obstruction produced by an aneurysm of the abdominal aorta, the authors add a third. The patient was admitted to the hospital because of vomiting which had persisted for several days. X-ray examination revealed narrowing of the third segment of the duodenum and dilatation in the first and second portions. At operation a fusiform aneurysm of the abdominal aorta was found, which compressed the retroperitoneal and fixed portion of the duodenum. An isoperistaltic duodenojejunostomy was

performed, and the patient made an uneventful recovery.

ABRAMSON

Merrill, D. L.: Mitral Valvulotomy in the Dog. Bull. Johns Hopkins Hosp. **87**: 21 (July), 1950.

Mitral valvulotomy was attempted in 47 dogs using a technic which directly exposed the attachment of the mitral valve without entering the heart cavities or interrupting the circulation. An incision was made in the auricular wall which extended to, but not through, the endocardium. A plane of cleavage was made between the endocardium and the auricular myocardium until the attachment of the valve was visible. The valve was not cut in 4 animals because the ring was inadequately exposed. Two dogs died at operation from uncontrollable hemorrhage. The valve was successfully cut in 41 of the animals.

In 10 dogs, lesions were selectively made through the valve at the anterior commissure. Nine animals survived, and 1 died of ventricular fibrillation immediately after the valve was cut. Pulmonary edema was not detected in these animals. After valvulotomy, a systolic thrill and murmur was always present, but there was little distention of the auricle. In 31 animals an attempt was made to produce a lesion through the center of the posterior leaflet. Such lesions produced in 22 dogs consistently produced severe mitral insufficiency; the auricle and the pulmonary veins ballooned out with each ventricular systole. Of thirteen of these dogs which were followed, four survived, and 9 died of pulmonary edema, 8 within five days, and 1 at six months.

The author concludes that division of the valve at the commissure produces less severe incompetence than division of a major leaflet.

MARGOLIES

Ada, A. E. W., Jones, O. R., and Sheeran, A. D.: Partial Pericardiectomy in a Case of Hemopericardium Due to Non-penetrating Trauma. J. Thoracic Surg. **20**: 105 (July), 1950.

This is a report of a case of pericardiectomy in a patient who suffered a hemorrhagic pericardial effusion with symptoms of cardiac tamponade. About five days before the onset of symptoms, the patient was kicked in the chest while playing with his 3 year old daughter. Immediately thereafter, he experienced severe tearing chest pain. X-ray examination showed an enlarged cardiac silhouette and the electrocardiogram showed low voltage QRS complexes with T-wave inversion in leads I, II, and III. Several pericardial aspirations yielded bloody fluid negative for tumor cells, pyogens, and acid fast organisms. Exploratory pericardiotomy was done to determine the cause of persistent bleeding. At operation the pericardium was bulging and thickened, and the visceral and parietal pericardium was covered by a granulation tissue which bled freely. Adhesions between visceral and parietal pericardium were severed, and two-thirds of the anterior pericardium overlying the ventricles was removed. The authors state that this is the first case of pericardectomy for nonpenetrating trauma to the chest.

KLOSK

THROMBOEMBOLIC PHENOMENA

Boyd, A. M.: External Iliac Artery Thrombosis. Brit. M. J. 4668: 1457 (June), 1950.

The author reports 2 cases of external iliac artery thrombosis, 1 of which followed trauma to the thigh, while in the other no previous history of value was elicited. Both patients suffered from intermittent claudication and showed a decrease in the oscillometric readings in the involved extremity after exercise. The normal limb in each instance demonstrated an increase under these circumstances.

In both cases an arteriectomy was performed, and the thrombosed segment of artery was removed. A lumbar sympathectomy was then carried out. One patient, examined a year after operation, showed a definite increase in the ability to walk. The other was seen again four months postoperatively; little change had occurred in the symptoms elicited by exercise. In both instances, exercise caused the pulsations in the involved limb to become palpably stronger, whereas preoperatively the converse had been observed. The important collateral circulation after occlusion of the external iliac artery is through the gluteal and obturator arteries and the spinous and cruciate anastomoses. The afferent vessels to these anastomoses arise from the internal iliac and occasionally the common iliac arteries.

ABRAMSON

Shepherd, J. T.: The Blood Flow through the Calf After Exercise in Subjects with Arteriosclerosis and Claudication. Clin. Sc. **9**: 49, 1950.

The effect of exercise on blood flow in the calf muscles was studied in 24 patients with intermittent claudication as a result of arteriosclerosis obliterans. A celluloid plethysmograph with air recording was used. The patients were divided into two groups depending upon the type of blood flow response observed in the postexercise period. In group A the immediate postexercise flow was found to be lower than that of normal individuals; the peak was followed by a gradual decline to the resting level. Ischemic exercise carried on to claudication did not increase the immediate postexercise flow; normal subjects showed a marked augmentation of circulation under these circumstances. In group B, the flow gradually increased, reaching a maximum some time in the postexercise period. The height of the peak was lower than that in group A. Removal of vasomotor tonus, by means of sympathectomy. indirect heating, intravenous injection of tetraethyl-

ammonium bromide, or paravertebral block had no effect on the pattern of blood flow following exercise. In other words, the sympathetic nervous system did not appear to play any role in altering the vascular response to exercise in patients with arteriosclerosis obliterans.

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VASCULAR DISEASE

Russell, J. Y. W.: Inferior Mesenteric Vascular Occlusion. Brit. J. Surg. **37**: 321 (Jan.), 1950.

The author describes a case of inferior mesenteric artery thrombosis with the production of an anemic infarct. This appears to be relatively rare as compared with occlusion of the superior mesenteric artery. The patient was a 73 year old woman who, while in the hospital for the amputation of a gangrenous lower extremity, developed severe lower abdominal pain and vomited twice. Shortly afterward she went into shock. Considerable tenderness and rigidity were present in the lower portion of the abdomen. Feces were present in the vagina, and on the posterior wall there was a small fistulous opening. At operation, performed 6 hours after the onset of symptoms, the large gut was found to be flaccid and gray in color. Resection of the nonviable bowel was carried out and a terminal colostomy was produced. However, the patient died 13 days later.

It is believed that the thrombosis of the inferior mesenteric artery was due to the marked atheroma present in the trunk of the main vessel. Rarely does an embolus enter this vessel because of its small diameter and the nature of its origin. On the other hand, since the superior mesenteric artery is larger, and at its origin runs almost parallel to the aorta, it is more often occluded by an embolus.

ABRAMSON

AMERICAN HEART ASSOCIATION, INC.

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Telephone Plaza 7-2045

FELLOWSHIP AWARDS

The Board of Directors, on recommendation of the Research Committee of the Scientific Council, has approved forty-one Fellowship Awards totaling $173,800 for 1951–52. These included the continuation of four Established Investigatorships, eight New Established Investigatorships, thirteen Research Fellow renewals, and sixteen new Research Fellows.

In addition, the following statement on the military status of applicants was approved: "In the event that a Fellow (Established Investigator) goes into non-permanent military service either before the beginning of his award or during its tenure, the total funds appropriated for one year, or the balance of such appropriated funds for that given year, shall be held in reserve until termination of military service. It will be the policy of the American Heart Association to encourage the completion of this Fellowship (Investigatorship) upon the termination of service, if circumstances warrant. The completion of the Fellowship (Investigatorship) will be subject to review with the Fellow (Investigator) every two years."

The Fellowship Awards were made as follows:

Continued Established Investigators

Bloch, Edward M., Chicago, the living microscopic blood, blood flow, and vessel walls in patients and experimental animals with thromboembolic phenomena, Western Reserve University.

Elkinton, J. Russell, Philadelphia, cardiovascular physiology, University of Pennsylvania.

Merrill, John P., Waban, Mass., further development of the artificial kidney as a therapeutic and investigative tool in cardiovascular and renal disease, Peter Bent Brigham Hospital, Boston.

Mommaerts, Wilfried F. H. M., Durham, N. C., biochemistry of muscular contraction, Duke University.

New Established Investigators

Dow, James W., Boston, peripheral and central mechanisms controlling the circulation, Childrens Medical Center and Harvard School of Public Health.

Fishman, Alfred P., Boston, cardiodynamic and renal interplay in the production of congestive heart failure, Mount Sinai Hospital, New York.

Gergely, John, Silver Spring, Md., energetics and contractile proteins of heart muscle, National Institutes of Health.

Heller, John H., Wilton, Conn., metabolic and endocrine basis of hypertension and arteriosclerosis, Yale University.

Kielley, W. Wayne, Boston, enzymes involved in oxidative phosphorylation, Tufts College.

Olson, Robert E., Needham, Mass., metabolism of cardiac muscle under various conditions of nutrition and endocrine balance, Harvard School of Public Health.

Stetson, Chandler A., New York, investigations in rheumatic fever, The Hospital of the Rockefeller Institute of Medical Research.

Tobian, Louis, Jr., Dallas, relations of steroids and sodium to hypertension; the role of steroid intoxication in toxemia of pregnancy; the role of emulsifying forces in plasma in atherosclerosis, University of Texas.

Renewal Research Fellows

Aikawa, Jerry K., Winston-Salem, N. C., under George T. Harrell, Bowman Gray School of Medicine.

Capps, Robert T., Madison, Wis., under O. S. Orth, University of Wisconsin.

Edelman, Isidore S., Brighton, Mass., under Francis D. Moore, Harvard University.

Fortier, Claude, Montreal, under Hans Selye, University of Montreal.

Horlick, Louis, Montreal, under Kenneth A. Evelyn, McGill University.

Hurst, William W., Great Falls, Mont., under Howard P. Lewis, University of Oregon.

Jorgens, Joseph, Minneapolis, under Leo G. Rigler, University of Minnesota.

Miller, Joseph H., Los Angeles, under Harry Goldblatt, Cedars of Lebanon Hospital.

Paterson, Philip Y., New Orleans, under Barry Wood, Washington University, St. Louis.

Roberts, Kathleen E., New York, under Robert F. Pitts, Cornell University.

Schieve, James F., Durham, N. C., under Eugene A. Stead, Jr., Duke University.

Schnabel, Truman G., Jr., Philadelphia, under Charles C. Wolferth, University of Pennsylvania.

White, Abraham G., New York, under Louis Leiter, Montefiore Hospital, New York.

New Research Fellowships

Alexander, James K., New York, under Eugene M. Landis, Harvard University.

Cavert, Henry M., Minneapolis, under Maurice B. Visscher, University of Minnesota.

Conn, Hadley L., Jr., Philadelphia, under Carl J. Schmidt, University of Pennsylvania.

Fowler, Noble O., Jr., Cincinnati, under Johnson McGuire, Cincinnati General Hospital.

Hackel, Donald B., Cleveland, under Thomas D. Kinney, City Hospital, Cleveland.

Haddy, Francis J., Rochester, Minn., under Maurice B. Visscher, University of Minnesota.

Hogness, John R., Seattle, under Robert H. Williams, University of Washington, Seattle.

Khairallah, Philip A., New York, under Wilfried F. H. M. Mommaerts, Duke University

Landon, Erwin J., Berkeley, Calif., under David M. Greenberg, University of California.

Lewis, Benjamin M., Boston, under Lewis Dexter, Peter Bent Brigham Hospital.

Nelson, Clifford V., London, England, under E. C. Cherry, Imperial College and W. F. Floyd, Middlesex Hospital Medical School, London.

Osborn, John J., Woodbury, N. Y., under L. Emmett Holt, Jr., New York University-Bellevue Medical Center.

Sanadi, D. Rao, Madison, under David E. Green, Institute for Enzyme Research, University of Wisconsin.

Schwartz, Irving L., New York, under Vincent P. Dole, Jr., The Hospital of the Rockefeller Institute for Medical Research.

Snively, George C., Minneapolis, under Cecil J. Watson, University of Minnesota.

Stefanini, Mario, Boston, under William Dameshek, New England Center Hospital.

ANNUAL MEETING SCHEDULE

Following is the schedule of meetings and events for the Association's Annual Meeting and Scientific Sessions to be held in Atlantic City, N. J., June 3–10, 1951.

Hotel Morton

Sunday, Monday and Tuesday, June 3–5
Staff Conference of Heart Associations and In-Service Training Sessions.
Tuesday, 2:00 P.M., June 5
Panel discussion on a timely topic sponsored by Staff Conference open to all members of A.H.A.

Chalfonte-Haddon Hall Hotel

Wednesday, 2:00 P.M., June 6
Assembly Panel Groups
Thursday, 8:00 A.M., June 7
Executive Committee
Thursday, 10:00 A.M., June 7
Assembly
Thursday, 2:00 P.M., June 7
Board of Directors
Friday and Saturday, 9:00 A.M. to 5:00 P.M., June 8, 9
Scientific Sessions
Friday, 12:00, June 8
Annual meeting of members
Saturday, 7:30 P.M., June 9
Annual Dinner
Sunday, 10:00 A.M., June 10
Scientific Council

PREVENTION OF CHRONIC ILLNESS

A National Conference to explore ways of preventing chronic disease, including cardiovascular disease, will be held in Chicago March 12–14 under the joint sponsorship of the Commission on Chronic Illness, the National Health Council, and the U. S. Public Health Service. Further details may be obtained from Dr. Morton L. Levin, Conference Director, 535 Dearborn Street, Chicago.

YOUNGSTOWN RESEARCH CONTRIBUTION

The Youngstown Area Heart Association has contributed $12,600 to the Research Fund of the American Heart Association. This amount is over and above the affiliate's regular contribution to the Association from its 1950 campaign.

CENTRAL OHIO FELLOWSHIP

The Central Ohio Heart Association has established a one-year Fellowship at Ohio State University College of Medicine. The basic requirements are: Graduation from a recognized medical college, one year rotating internship, two years residency in medicine, and one year residency in cardiology. The Fellowship stipend is $3,600 per annum and it will start July 1, 1951. Applications should be sent to Dr. R. W. Kissane, 9 Buttles Avenue, Columbus, Ohio, before April 1.

ELECTROCARDIOGRAPHIC INTERPRETATION

A twelve-week course in Electrocardiographic Interpretation for graduate physicians is being started this month at the Michael Reese Memorial Postgraduate School. The class will be conducted by Dr. Louis N. Katz, Director of Cardiovascular Research, every Wednesday from 7:00 to 9:00 P.M., beginning February 7.

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Circulation

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